REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Chromosomal Abnormalities in Cancer

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Cytogenetic abnormalities are a characteristic attribute of cancer cells. To date, clonal chromosome aberrations have been found in all major tumor types from more than 54,000 patients (http://cgap.nci.nih.gov/Chromosomes/Mitelman), and their identification continues as a result of technical improvements in conventional and molecular cytogenetics. The World Health Organization Classification of Tumours recognizes a growing number of such genetic changes and uses them to define specific disease entities. Many of these aberrations have emerged as prognostic and predictive markers in hematologic cancers and certain types of solid tumors. Furthermore, the molecular characterization of cytogenetic abnormalities has provided insights into the mechanisms of tumorigenesis and has, in a few instances, led to treatment that targets a specific genetic abnormality. This article discusses examples of two main classes of chromosomal abnormalities — balanced chromosomal rearrangements and chromosomal imbalances (Fig. 1 and 2) — with particular focus on their functional consequences and their implications (actual or potential) for the development of effective anticancer therapies.

CAUSES OF CHROMOSOMAL ABNORMALITIES

The cause of chromosomal abnormalities remains poorly understood. Studies of various types of leukemia have shown that certain environmental and occupational exposures and therapy with cytotoxic drugs can induce chromosomal aberrations. For example, cases of the myelodysplastic syndrome or acute myeloid leukemia that arise after treatment with alkylating agents are frequently associated with unbalanced abnormalities, primarily deletion or loss of chromosome 5 or 7 (or both), whereas therapy with topoisomerase II inhibitors is typically associated with balanced abnormalities, most commonly translocations involving the *MLL* gene on chromosome band 11q23.[1] For most cancer-associated chromosomal abnormalities, however, no specific initiating factor has been identified.

Insights into molecular mechanisms underlying the formation of chromosomal aberrations have been gained from studies of rare cancer-predisposing chromosomal instability syndromes, such as the inherited bone marrow failure syndromes,[2] in which genetic changes that are associated with the development of leukemia can be followed over time. Cases of the myelodysplastic syndrome or acute myeloid leukemia arising in patients with Fanconi's anemia, for example, typically have complex, unbalanced chromosomal abnormalities, which are thought to result from inactivation of components of the Fanconi's anemia pathway that regulates the recognition and repair of damaged DNA.[3] The complex genetic changes in Fanconi's anemia appear to be preceded by isolated focal gains or cryptic rearrangements of chromosome band 3q26 that cause overexpression of the *EVI1* gene.[4] This early genetic event may have a role in the development of cancers that result from a constitutional imbalance between genotoxic stress and DNA repair. Whether similar mechanisms are relevant to the pathogenesis of chromosomal abnormalities that are

associated with sporadic cancers remains to be determined. (The full names of all genes that are mentioned in this review are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

CHROMOSOMAL REARRANGEMENTS

Reciprocal translocations, inversions, and insertions are typical chromosomal rearrangements. There is substantial evidence that these alterations are early or even initiating events in tumorigenesis. For instance, certain translocations that are associated with childhood leukemia arise in utero, years before the appearance of overt disease.[5] Furthermore, most chromosomal rearrangements are closely associated with specific tumor types, even though individual genes — such as *MLL*, *ETV6*, and *NUP98* — can participate in multiple different translocations, sometimes with distinct clinicopathological associations.[6] Notably, certain chromosomal rearrangements, such as the *BCR-ABL1* fusion gene, serve as sensitive indicators in the assessment of the response to cancer treatment.[7]

With regard to their functional consequences, recurrent chromosomal rearrangements are of two general types: aberrations that result in the formation of a chimeric fusion gene with new or altered activity and chromosomal changes that lead to deregulated expression of a structurally normal gene (Fig. 2 and 3). Table 1 lists examples in these two functional categories.

Until recently, chromosomal rearrangements have been linked mainly to hematologic cancers and tumors of mesenchymal origin.[8,9] However, a number of recent studies have shown that genomic rearrangements that juxtapose two genes also play major roles in the pathogenesis of epithelial cancers, such as prostate cancer and non–small-cell lung cancer.[10,11] It is possible that similar rearrangements in other solid tumors exist but have escaped notice because of technical problems, such as the difficulty in growing tumor cells for chromosomal analysis, or because they are cytogenetically invisible or masked by multiple complex and often nonspecific karyotypic changes, which are thought to reflect secondary genetic events acquired during tumor progression.

CHIMERIC FUSION GENES

The majority of chromosomal rearrangements result in the formation of a chimeric gene through the fusion of parts of two genes. The two main groups of genes that participate in such fusions are those encoding tyrosine kinases and those encoding transcription factors.

Tyrosine Kinase Genes

The classic example of a cytogenetic abnormality leading to the formation of a chimeric fusion gene is the Philadelphia chromosome,[12] a truncated chromosome 22 that is present in virtually all patients with chronic myeloid leukemia, in approximately 20% of patients with acute lymphoblastic leukemia, and in rare cases of acute myeloid leukemia. The Philadelphia chromosome is the result of a reciprocal translocation, t(9;22)(q34.1;q11.23),[13] in which sequences of the *BCR* gene on band 22q11.23 are joined to portions of the gene encoding the cytoplasmic ABL1 tyrosine kinase on band 9q34.1 (Fig. 3A; for an explanation of the nomenclature used for translocations, inversions, monosomies, trisomies, deletions, derivative chromosomes, and additional material of unknown origin, see the Supplementary Appendix).[14-16] The resulting chimeric protein, BCR-ABL1, contains the catalytic domain of ABL1 fused to a domain of BCR that mediates constitutive oligomerization of the fusion protein in the absence of physiologic activating signals, thereby promoting aberrant tyrosine kinase activity.[17]

The discovery of the Philadelphia chromosome and the understanding of its molecular basis have had far-reaching implications. First, these findings provided evidence that human cancer can arise from acquired genetic alterations in somatic cells. Second, the aberrant tyrosine kinase signaling in chronic myeloid leukemia led to the use of a selective tyrosine kinase inhibitor, imatinib mesylate, to treat the disease.[18,19] Third, imatinib-resistant kinase domain mutations have been identified as a major cause of relapse during imatinib therapy,[20] and this finding, in turn, has led to the development of second-generation BCR-ABL1 inhibitors, such as dasatinib and nilotinib.[21-24]

In addition to t(9;22)(q34.1;q11.23), several other translocations form tyrosine kinase fusion proteins with constitutive enzymatic activity,[25] and some of these fusions also confer sensitivity to tyrosine kinase inhibitors (Table 1).[26,27] These observations highlight the usefulness of conventional chromosomal analysis for guiding the development of new anticancer agents, but the advent of molecular cytogenetic techniques, such as fluorescence in situ hybridization,[28] has further improved the detection of genomic rearrangements that

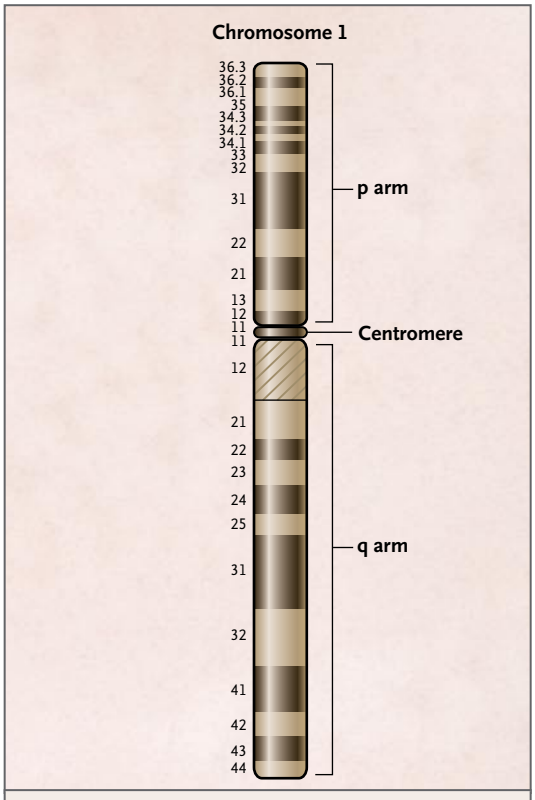

Figure 1. Structure of a Human Chromosome.

Each human chromosome, shown here at a resolution of 400 bands per haploid genome, contains two specialized structures, a centromere and two telomeres. The centromere divides the chromosome into short (p) and long (q) arms and is essential for the segregation of chromosomes during cell division. The telomeres "cap" the p and q arms and are important for the structural integrity of the chromosome, for complete DNA replication at the ends of the chromosome, and for the establishment of the three-dimensional architecture of the nucleus. Chromosomes are isolated at the metaphase or prometaphase stage of the cell cycle and are treated chemically (e.g., by enzymatic digestion and staining with a DNA-binding dye) to reveal specific patterns of light and dark bands that are microscopically visible. Analysis of the distribution of bands on individual chromosomes allows the identification of structural chromosomal abnormalities.

could serve as the basis for new treatments.[29-31] Molecular cytogenetic analyses have revealed, for example, that approximately 5% of adults with T-cell acute lymphoblastic leukemia harbor an imatinib-sensitive fusion of *ABL1* to the *NUP214* gene on band 9q34.1. This fusion occurs on episomes — extrachromosomal elements that are invisible by standard cytogenetic analysis.[31]

Constitutively activated tyrosine kinases also drive many types of epithelial cancers.[25] Point mutation or genomic amplification of tyrosine kinase genes have been well documented as mechanisms underlying aberrant tyrosine kinase activity in epithelial tumors.[25] Nevertheless, the rarity of cytogenetically visible rearrangements has led to the commonly held belief that tyrosine kinase fusion proteins have no major role in the pathogenesis of carcinomas. This view has recently been challenged by the discovery of a cryptic inversion — inv(2)(p22-p21p23) — in 6.7% of Japanese patients with non–small-cell lung cancer, which results in the formation of a fusion gene comprising portions of *EML4* and the gene encoding the ALK receptor tyrosine kinase.[32]

Transcription Factor Genes

Chromosomal rearrangements that disrupt transcription factor genes can result in fusion proteins with enhanced or aberrant transcriptional activity or fusion proteins that mediate transcriptional repression. A fusion protein with enhanced or aberrant transcriptional activity is present in virtually all cases of Ewing's sarcoma, in which unique translocations — t(11;22)(q24.1-q24.3;q12.2) and t(21;22)(q22.3;q12.2) — fuse the *EWSR1* gene on band 22q12.2 to a gene encoding a member of the ETS family of transcription factors, most frequently *FLI1* on band 11q24.1-q24.3 (in approximately 85% of patients) and *ERG* on band 21q22.3 (in approximately 10% of patients) (Fig. 3B).[33,34] The resulting chimeric transcription factors retain the DNA-binding domain of the respective ETS family member and possess, in the EWSR1 portion of the fusion protein, a potent transactivation domain that induces the transcription of various genes whose aberrant expression appears to be required for EWSR1-ETS–mediated tumor growth.[35,36]

The functional role of many oncogenic transcription factors has been well characterized. Even so, selective inhibition of the abnormal transcriptional activity has proved to be a less tractable pharmacologic goal than inhibition of constitutive tyrosine kinase activity.[37] As a consequence, approaches to specific targeting of overactive transcription factors have not yet reached clinical development.

Chromosomal rearrangements that entail aberrant transcriptional repression occur in a substantial proportion of patients with acute myeloid leukemia.[38] For example, the chimeric proteins resulting from fusion genes such as *PML-RARA*

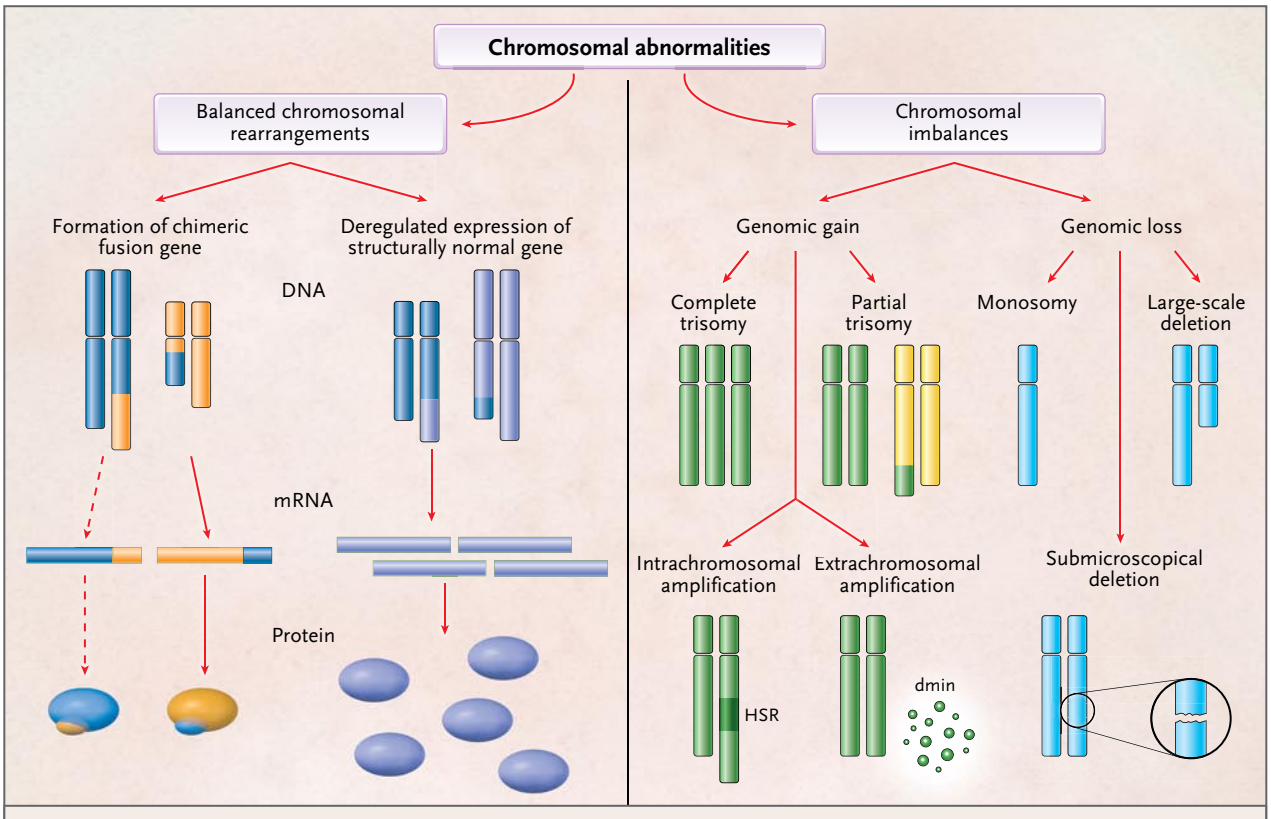

Figure 2. Chromosomal Abnormalities in Human Cancer.

The two main classes of chromosomal abnormalities found in human cancer are shown. Balanced chromosomal rearrangements can be categorized into those that lead to the formation of a chimeric fusion gene and those that lead to the aberrant juxtaposition of gene regulatory elements to the coding sequence of a structurally intact gene. The formation of a chimeric fusion gene results in the expression of a chimeric protein with new or altered activity. In the majority of cases, only one of the two fusion genes generated and not the reciprocal counterpart (indicated by the dashed arrows) contributes to cancer pathogenesis. The deregulated expression of a structurally normal gene results in deregulated expression of a normal protein. Chromosomal imbalances can be categorized into genomic gains and genomic losses. Genomic gains include complete or partial trisomies and intrachromosomal or extrachromosomal amplifications, which can be identified cytogenetically as homogeneously staining regions (HSR) and double-minute chromosomes (dmin), respectively. HSR are chromosomal regions that display no typical banding pattern; dmin are circular, acentric, autonomously replicating DNA strands of varying size; mRNA denotes messenger RNA. Genomic losses include monosomies and large-scale or submicroscopical deletions.

(Fig. 3C), *RUNX1-RUNX1T1*, and *CBFB-MYH11* all contain a transcription factor that retains its DNA-binding motif and an unrelated protein that interacts with inhibitors of gene transcription. As a result, binding of the chimeric transcription factors to their target genes, which include genes required for normal myeloid differentiation, causes aberrant transcriptional repression, thereby contributing to the accumulation of immature myeloid cells in acute myeloid leukemia.[39]

One of the fusion proteins associated with transcriptional repression has been targeted with success in the clinic. In acute promyelocytic leukemia, all-*trans* retinoic acid and arsenic trioxide reverse the transcriptional repression caused by the PML-RARA fusion protein by forcing the release of transcription inhibitors from the fusion protein or stimulating degradation of PML-RARA or both. These two drugs are remarkably effective in acute promyelocytic leukemia.[40-42]

DEREGULATION OF EXPRESSION OF NORMAL GENES

Chromosomal rearrangements that juxtapose tissue-specific regulatory elements, such as gene promoters or enhancer sequences, to the coding sequence of a proto-oncogene deregulate expression of the proto-oncogene. This abnormality is exemplified by the reciprocal translocations associated with Burkitt's lymphoma, in which the enhancer of an immunoglobulin gene (*IGHG1*, band 14q32.33;

Table 1. Selected Examples of Chromosomal Rearrangements.*

Genetic Change†	Gene Fusion	Disease	Targeted Therapy‡
Formation of chimeric fusion genes			
Involving tyrosine kinases			
inv(2)(p22-p21p23)§	*EML4-ALK*	Non–small-cell lung cancer	
t(2;5)(p23;q35)	*ALK-NPM1*	Anaplastic large-cell lymphoma	
t(4;14)(p16.3;q32.33)§	*WHSC1-IGHG1*	Multiple myeloma	
del(4)(q12q12)§	*FIP1L1-PDGFRA*	Myeloid neoplasm associated with eosinophilia	Imatinib
t(5;12)(q31-q32;p13)	*PDGFRB-ETV6*	Myeloid neoplasm associated with eosinophilia	Imatinib
t(9;22)(q34.1;q11.23)	*BCR-ABL1*	Chronic myeloid leukemia, acute lymphoblastic leukemia, acute myeloid leukemia	Imatinib, dasatinib, nilotinib
episome(9q34.1)§	*NUP214-ABL1*	Acute lymphoblastic leukemia	Imatinib
inv(10)(q11.2q11.2)§	*RET-NCOA4*	Papillary thyroid cancer	
inv(10)(q11.2q21)	*RET-CCDC6*	Papillary thyroid cancer	
t(12;15)(p13;q25)	*ETV6-NTRK3*	Various cancers	
Involving transcription factors			
t(1;22)(p13;q13)	*RBM15-MKL1*	Acute megakaryoblastic leukemia	
t(2;3)(q12-q14;p25)	*PAX8-PPARG*	Follicular thyroid cancer	
t(7;11)(p15-p14;p15.5)	*NUP98-HOXA9*	Myelodysplastic syndrome, acute myeloid leukemia	
t(8;21)(q22;q22.3)	*RUNX1-RUNX1T1*	Acute myeloid leukemia	
t(9;11)(p22;q23)	*MLL-MLLT3*	Acute myeloid leukemia	
t(11;22)(q24.1-q24.3;q12.2)	*FLI1-EWSR1*	Ewing's sarcoma	
t(12;21)(p13;q22.3)§	*ETV6-RUNX1*	Acute lymphoblastic leukemia	
t(15;17)(q22;q21)	*PML-RARA*	Acute promyelocytic leukemia	All-*trans* retinoic acid, arsenic trioxide
inv(16)(p13.11q22.1)	*CBFB-MYH11*	Acute myeloid leukemia	
t(21;22)(q22.3;q12.2)	*ERG-EWSR1*	Ewing's sarcoma	
Deregulated expression of structurally normal genes			
t(8;14)(q24.21;q32.33)	*MYC-IGHG1*	Burkitt's lymphoma	
t(11;14)(q13;q32.33)	*CCND1-IGHG1*	Mantle-cell lymphoma	
t(12;13)(p13;q12.3)	*ETV6-CDX2*	Acute myeloid leukemia	
t(14;18)(q32.33;q21.3)	*IGHG1-BCL2*	Follicular lymphoma	
del(21)(q22.3q22.3)§	*TMPRSS2-ERG*	Prostate cancer	

* The full names of all genes that are listed according to their abbreviations appear in a glossary in the Supplementary Appendix.
† Chromosomal localizations are in accordance with the genome mapping data provided in the National Center for Biotechnology Information (NCBI) Map Viewer (build 36.3; www.ncbi.nlm.nih.gov/mapview).
‡ Imatinib has not been approved for treatment of myeloid neoplasms associated with eosinophilia and *NUP214-ABL1*–positive acute lymphoblastic leukemia, but therapeutic efficacy is predicted on the basis of preclinical studies. The other drugs listed have been approved for treatment of the indicated tumor types.
§ This cryptic alteration is cytogenetically invisible.

IGKC, 2p12; and *IGLC1*, 22q11.2) drives the constitutive expression of the gene encoding the MYC transcription factor on band 8q24.21 (Fig. 3D).[43]

Chromosomal changes that cause overexpression of structurally normal genes occur in other cancers of B-cell or T-cell origin[44] but were believed to be very rare in nonlymphoid cancers. This view has changed since the recent discovery that prostate cancer is associated with chromosomal rearrangements that bring about overexpression of members of the ETS family of transcription factors.[11] The most common of these rearrange-

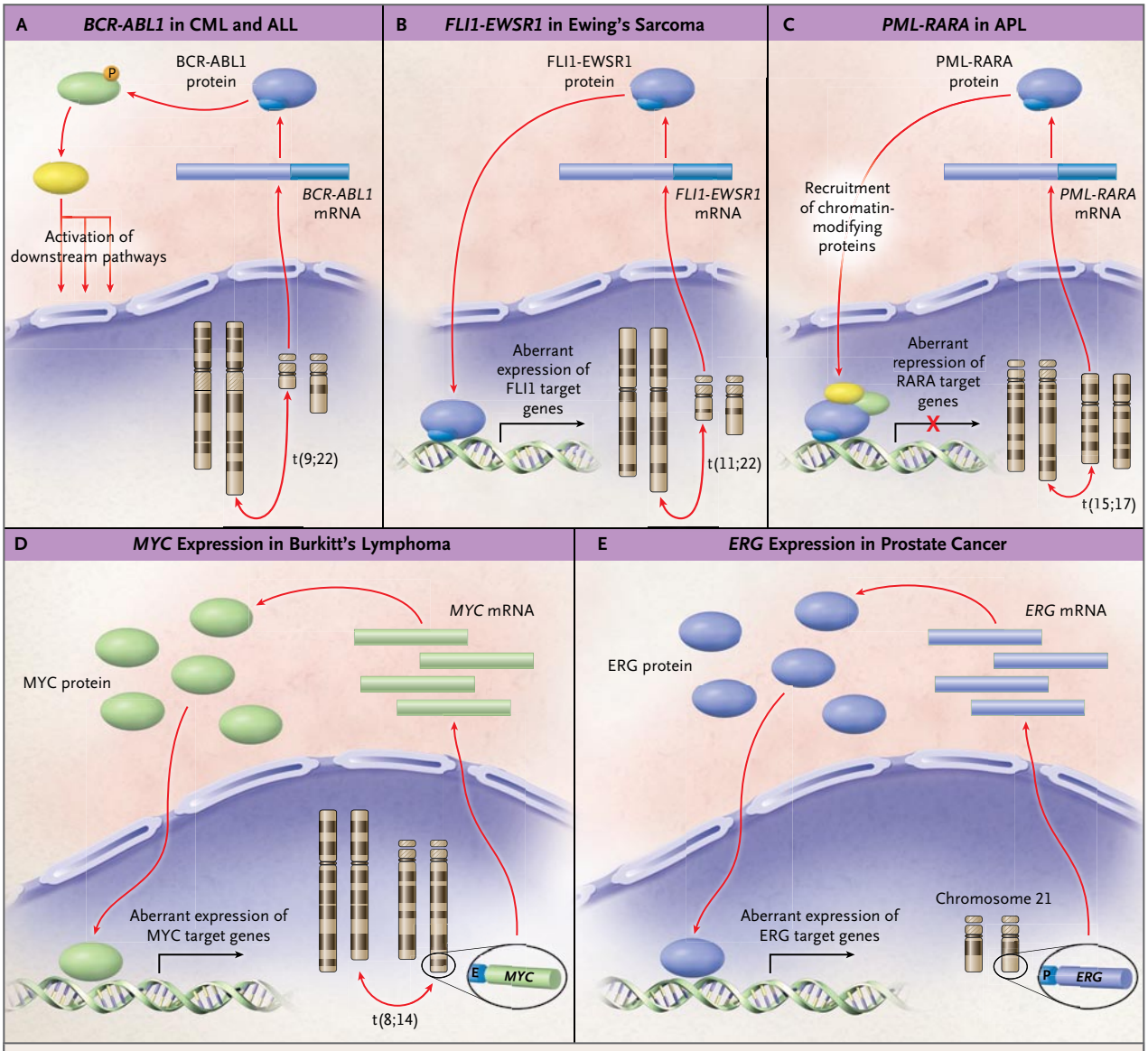

Figure 3. Functional Consequences of Balanced Chromosomal Rearrangements.

Panels A through C illustrate the functional consequences of different chromosomal rearrangements that result in the formation of a chimeric fusion gene. Rearrangements leading to the expression of a chimeric protein with constitutive tyrosine kinase activity in the absence of physiologic activating signals are represented by the translocation t(9;22)(q34.1;q11.23) associated with chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) (Panel A). Rearrangements leading to the expression of a chimeric protein with aberrantly increased transcriptional activity are represented by the translocation t(11;22)(q24.1-q24.3;q12.2) associated with Ewing's sarcoma (Panel B). Rearrangements leading to the expression of a chimeric protein that mediates aberrant transcriptional repression through interaction with chromatin-modifying proteins are represented by the translocation t(15;17)(q22;q21) associated with acute promyelocytic leukemia (APL) (Panel C). Panels D and E show different chromosomal rearrangements that result in deregulated expression of a structurally normal gene. In Burkitt's lymphoma, the translocation t(8;14)(q24.21;q32.33) leads to the aberrant juxtaposition of the enhancer (E) of the *IGHG1* gene on band 14q32.33 with the coding sequence of the *MYC* gene on band 8q24.21, resulting in overexpression of the MYC transcription factor in lymphoid tissues (Panel D). In prostate cancer, a small interstitial deletion or cryptic insertion involving chromosome band 21q22.3 fuses androgen-regulated sequences in the promoter (P) of the prostate-specific *TMPRSS2* gene to the coding region of the *ERG* gene, resulting in aberrant expression of the ERG transcription factor in prostate tissue (Panel E). The term mRNA denotes messenger RNA.

ments fuses all coding exons of the *ERG* gene to androgen-regulated sequences in the promoter of the prostate-specific *TMPRSS2* gene; these sequences mediate the aberrant expression of *ERG* in prostate tissue (Fig. 3E).[45,46] Both genes are located on band 21q22.3, approximately 3 Mb apart, and multiple genomic alterations, such as heterozygous and homozygous deletions or insertions, contribute to the formation of various *TMPRSS2-ERG* fusion transcripts.[45,47] In addition, fusions between other *ETS* family members and *TMPRSS2* and *ETS* rearrangements involving alternative fusion partners (including androgen-repressed and androgen-insensitive genes) occur.[46,48-50] It will be of prime importance to evaluate the use of these new genetic biomarkers for early detection and outcome prediction in prostate cancer.[51-54]

CHROMOSOMAL IMBALANCES

Chromosomal imbalances — gains or losses of genetic material — can range from alterations spanning entire chromosomes to intragenic duplications or deletions. Unlike rearrangements, in which the genes that become deregulated and the functional consequences of the rearrangements can be readily identified through analysis of the breakpoint regions, most chromosomal imbalances have functional consequences that are unknown. Determining the implications of some chromosomal gains or losses involving single genes has

Table 2. Selected Examples of Chromosomal Imbalances.*

Genetic Change†	Gene	Disease	Targeted Therapy‡
Genomic gains			
Unknown target genes			
+1q	?	Various cancers	
+7	?	Astrocytoma, glioblastoma	
+8	?	Myelodysplastic syndrome, acute myeloid leukemia	
+12	?	Chronic lymphocytic leukemia	
+12p	?	Testicular germ-cell tumor	
+17q	?	Various cancers	
Known target genes			
amp(1)(q32.1)	IKBKE	Breast cancer	
amp(2)(p24.1)	MYCN	Neuroblastoma	
amp(3)(p14.2-p14.1)	MITF	Malignant melanoma	
dup(6)(q22-q23)	MYB	Acute lymphoblastic leukemia	
amp(6)(q25.1)	ESR1	Breast cancer	Tamoxifen
amp(7)(p12)	EGFR	Various cancers	Cetuximab, panitumumab, gefitinib, erlotinib
amp(7)(q31)	MET	Various cancers	
amp(8)(q24.21)	MYC	Various cancers	
+9p	JAK2	Polycythemia vera	
amp(11)(q13)	CCND1	Various cancers	
amp(11)(q13-q22)	*YAP1*, *BIRC2*	Hepatocellular carcinoma	
amp(12)(p12.1)	KRAS	Various cancers	
amp(13)(q12.3)	CDX2	Acute myeloid leukemia	
amp(14)(q13)	NKX2-1	Non–small-cell lung cancer	
amp(17)(q21.1)	ERBB2	Various cancers	Trastuzumab, lapatinib
amp(21)(q22.3)	ERG	Acute myeloid leukemia	

Table 2. (Continued.)

Genetic Change†	Gene	Disease	Targeted Therapy‡
Genomic losses			
Unknown target genes			
del(1p)	?	Neuroblastoma, anaplastic oligodendroglioma	
del(3p)	?	Various cancers	
del(5q)	?	Myelodysplastic syndrome, acute myeloid leukemia	
del(6q)	?	Various cancers	
del(7q)	?	Myelodysplastic syndrome, acute myeloid leukemia	
del(11q)	?	Various cancers	
del(19q)	?	Anaplastic oligodendroglioma	
del(20q)	?	Polycythemia vera, myelodysplastic syndrome, acute myeloid leukemia	
Known target genes			
del(3p26-p25)	VHL	Renal-cell cancer	
del(4)(q12)	REST	Colon cancer	
del(5)(q21-q22)	APC	Colon cancer	
del(5)(q32)	RPS14	Myelodysplastic syndrome (5q minus syndrome)	Lenalidomide
del(7)(p13-p11.1)	IKZF1	*BCR-ABL1*–positive acute lymphoblastic leukemia, lymphoid blast crisis of chronic myeloid leukemia	
del(9)(p13)	PAX5	Acute lymphoblastic leukemia	
del(9)(p21)	CDKN2A/CDKN2B	Various cancers	
del(10)(q23.3)	PTEN	Various cancers	Sirolimus
del(11)(q22-q23)	ATM	Various cancers	
del(12)(p13)	ETV6	Acute myeloid leukemia, acute lymphoblastic leukemia	
del(13)(q14.2)	RB1	Retinoblastoma	
del(17)(p13.1)	TP53	Various cancers	
del(17)(q11.2)	NF1	Various cancers	
del(X)(q11.1)	FAM123B	Wilms' tumor	

* The full names of all genes that are listed according to their abbreviations appear in a glossary in the Supplementary Appendix.
† Chromosomal localizations are in accordance with the genome mapping data provided in the NCBI Map Viewer (build 36.3; www.ncbi.nlm.nih.gov/mapview).
‡ Tamoxifen, cetuximab, panitumumab, gefitinib, erlotinib, trastuzumab, lapatinib, and lenalidomide have been approved for treatment of the indicated tumor types; sirolimus (also called rapamycin) has not been approved as an anticancer agent, but therapeutic efficacy in *PTEN*-deficient tumors is predicted on the basis of preclinical and early clinical studies.

been relatively straightforward, but most imbalances affect large genomic regions containing multiple genes, and many tumors have numerous unbalanced chromosomal abnormalities. Although this degree of genetic complexity has hampered the delineation of the roles of individual chromosomal gains or losses in cancer, recent studies suggest that integration of genomewide analysis of gene dosage, global gene-expression profiling, and functional genomic techniques could identify functionally relevant genes within genomic regions that are affected by chromosomal imbalances.[55] Selective examples of chromosomal imbalances are listed in Table 2.

GENOMIC GAINS

Most recurrent genomic gains probably contribute to tumorigenesis by enhancing the activity of specific genes in the affected chromosomal regions. Some of these genes encode proteins that can be

specifically targeted by new anticancer agents. One example, which occurs in approximately 30% of women with breast cancer, is amplification of the gene on band 17q21.1 that encodes the ERBB2 receptor tyrosine kinase. The resulting overexpression of ERBB2 represents a target for the monoclonal antibody trastuzumab; the combination of trastuzumab with chemotherapy reduces the rate of death from breast cancer in both the adjuvant and metastatic settings.[56,57]

Large-Scale Genomic Gains

Genomic gains commonly arise from chromosomal nondisjunction or unbalanced translocations, which cause complete or partial chromosomal trisomies, or from amplification events affecting DNA segments of different size (Fig. 2). Numerous examples of large-scale genomic gains are associated with specific types of cancer (Table 2). Since such aberrations involve multiple genes, the identification of their functionally relevant targets has proved to be difficult. One way to "filter" the genes within regions of DNA copy-number gain is to identify those that are also altered at the RNA or protein level, assuming that genes whose increased dosage translates into increased expression are most likely to be involved in malignant transformation. This strategy has uncovered new oncogenes in malignant melanoma (*MITF* and *NEDD9* on bands 3p14.2-p14.1 and 6p25-p24, respectively)[58,59] and hepatocellular carcinoma (*YAP1* and *BIRC2* on bands 11q13 and 11q22, respectively)[60] and has identified candidate breast-cancer genes.[61,62]

Focal Genomic Gains

Gains affecting small genomic regions or even single genes have been described less frequently than large gains. However, it is now possible to identify focal gains by scanning cancer genomes for variations in DNA copy numbers with new high-resolution methods, such as comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) genotyping.[63,64] Array-based CGH and SNP genotyping analyses, for example, have shown amplification of a small segment of band 6q25.1 containing the gene encoding estrogen receptor 1 (*ESR1*) in a subgroup of women with breast cancer, although additional studies will be required to determine the exact frequency of these amplifications as well as their clinical ramifications.[65,66] These amplifications correlate with increased ESR1 protein levels, and preliminary clinical data suggest that *ESR1* amplification is associated with increased sensitivity to tamoxifen.[65]

The power of high-resolution SNP arrays to identify focal genomic gains is also illustrated by a recent study that revealed amplification of a 480-kb interval on band 14q13, comprising two known genes, in approximately 12% of patients with non–small-cell lung cancer.[67] Subsequent functional studies identified the *NKX2-1* gene, which encodes a lung-specific transcription factor, as an oncogene that may be involved in this focal event.

The analysis of genes that are recurrently amplified in tumors can also reveal alternative pathogenetic mechanisms that can be exploited therapeutically, as exemplified by the identification of point mutations in the catalytic domain of the EGFR receptor tyrosine kinase in patients with non–small-cell lung cancer that are associated with responsiveness to the kinase inhibitors gefitinib and erlotinib.[68] By contrast, genomic gains can also underlie acquired resistance to targeted cancer therapy, as exemplified by the recent discovery that amplification and overexpression of the gene encoding the MET receptor tyrosine kinase on band 7q31 can restore aberrant signal transduction downstream of mutant EGFR in non–small-cell lung cancer cells treated with an EGFR inhibitor.[69]

GENOMIC LOSSES

The spectrum of genomic losses ranges from cytogenetically visible alterations, such as complete or partial chromosomal monosomies, to single-gene or intragenic deletions that are detectable only by techniques that provide high spatial resolution. Most recurrent genomic losses probably contribute to malignant transformation by reducing the function of specific genes in the affected chromosomal regions. Since restoration of gene function is more challenging than, for example, inhibition of increased kinase activity, it is unclear whether direct pharmacologic targeting of genomic losses will ever be possible. Nevertheless, an improved understanding of the functional consequences of these aberrations may lead to the identification of indirect targets for therapeutic intervention. For example, inactivation of the *PTEN* tumor-suppressor gene on band 10q23.3, which occurs with high frequency in glioblastoma, prostate cancer, and endometrial cancer,[70]

increases signaling through the phosphoinositide-3-kinase–AKT–mammalian target of rapamycin (PI3K–AKT–mTOR) pathway and promotes tumor-cell proliferation and survival. Experimental models and early clinical trials indicate that *PTEN*-deficient tumors are sensitized to the growth-suppressive activity of mTOR inhibitors, such as sirolimus (also called rapamycin).[71-73]

The dissection of the mechanisms through which genomic losses promote tumorigenesis is challenging. Recent developments include the application of modern genomic techniques to the study of large-scale genomic losses, the identification of new tumor-suppressor genes that act through allelic insufficiency, and the discovery of noncoding genes as functionally relevant targets of recurrent genomic losses.

Large-Scale Genomic Losses

Extensive genomic deletions affecting multiple genes are frequent in tumors, making it difficult to identify which lost gene contributes to the development of the cancer. The classic approach to identifying a tumor-suppressor gene compares multiple tumors with a specific chromosomal deletion to determine the minimal genomic region that is lost in all cases. Candidate genes from this region are then screened for deletions, mutations, or epigenetic modifications that inactivate the remaining allele.[74,75] This strategy has identified important tumor-suppressor genes such as *RB1* (band 13q14.2), *TP53* (17p13.1), *APC* (5q21-q22), *NF1* (17q11.2), *PTEN* (10q23.3), and *ATM* (11q22-q23).

For many recurrent genomic losses, however, such as 1p deletions in neuroblastoma,[76] 3p deletions in lung cancer,[77] and 7q deletions in myeloid cancers,[78,79] the critical genes are unknown. Regardless of whether the respective disease genes have been identified, some deletions have proved to be of great value for determining the prognosis and guiding treatment decisions, as exemplified by the deletion of chromosome 5q in acute myeloid leukemia[38]; deletions of chromosomes 11q, 13q, and 17p in chronic lymphocytic leukemia[80]; and the concurrent deletion of chromosomes 1p and 19q in anaplastic oligodendroglioma.[81]

New genomic techniques have considerably improved the identification of functionally relevant genes within regions of recurrent chromosomal deletions. For example, RNA interference screening in combination with high-resolution DNA copy-number analysis identified the *REST* gene as a suppressor of epithelial-cell transformation that maps to a segment of band 4q12 that is frequently deleted in colon cancer.[82] The power of array-based SNP genotyping as a tool for gene discovery in cancers associated with genomic losses is demonstrated by recent studies that revealed deletions of *PAX5* (band 9p13) and *IKZF1* (7p13-p11.1) in approximately 30% of children with B-progenitor acute lymphoblastic leukemia and in more than 80% of patients with *BCR-ABL1*–positive acute lymphoblastic leukemia, respectively.[83,84]

Genomic Losses Resulting in Allelic Insufficiency

Another difficulty in the analysis of chromosomal deletions occurs in the identification of genes that contribute to tumorigenesis by inactivation of a single allele.[85] Since such haplo-insufficient tumor-suppressor genes cannot be identified through analysis of the remaining allele, alternative approaches are required to assess the consequences of monoallelic deletion. An example is a recent study in which graded down-regulation of multiple candidate genes by RNA interference was used to identify *RPS14* as a causal gene for the 5q minus syndrome,[86] a subtype of the myelodysplastic syndrome characterized by a 1.5-Mb commonly deleted region on chromosome band 5q32.[87] Notably, patients with the 5q minus syndrome are highly responsive to the thalidomide derivative lenalidomide,[88] although the mechanisms through which lenalidomide restores normal erythropoiesis remain unknown.

Monoallelic deletions can completely inactivate tumor-suppressor genes that are located on the X chromosome because humans carry only one functional copy of all X-linked genes. This mechanism was documented in a recent study that identified small deletions of band Xq11.1, targeting the *FAM123B* tumor-suppressor gene, in 21.6% of patients with sporadic Wilms' tumors.[89] DNA sequence analysis subsequently identified additional patients with inactivating *FAM123B* mutations,[89] again highlighting the potential of chromosomal imbalances for guiding the discovery of alternative genetic changes with similar functional consequences.

Genomic Losses Affecting Noncoding Genes

Cancer-associated chromosomal losses may act through inactivation of genes that do not encode proteins. For example, several genomic regions that are recurrently deleted in a variety of tumors con-

tain microRNA genes.[90,91] These genes encode small RNAs involved in post-transcriptional regulation of gene expression, and there is growing evidence that the loss of specific microRNAs with tumor-suppressive activity may contribute to tumorigenesis. This pathogenetic mechanism was shown by the observation that *MIRN15A* and *MIRN16-1* are located within a segment of band 13q14.3 that is deleted in approximately 50% of patients with chronic lymphocytic leukemia[92] and the subsequent discovery that *MIRN15A* and *MIRN16-1* negatively regulate the expression of the antiapoptotic protein BCL2.[93] Given that many chromosomal regions that are recurrently deleted in cancer appear to lack protein-coding genes that normally act to limit cell proliferation, it seems plausible that the analysis of cancer-associated genomic losses will reveal additional tumor-suppressor microRNAs.

SUMMARY

Cancer is caused by genetic alterations that disrupt the normal balance among cell proliferation, survival, and differentiation. The examples described here illustrate that many of these alterations are mediated by genetic changes associated with chromosomal abnormalities. Of particular importance for the treatment of cancer, many of the most specific drug targets, such as *ABL1*, *ERBB2*, and *EGFR*, undergo genetic changes that conventional cytogenetic methods or modern genomic techniques can detect. Therefore, the analysis of chromosomal abnormalities can be used to identify the subpopulation of patients who are most likely to benefit from a particular drug treatment.

However, the strategy of gene-targeted therapy has thus far had limited application, because only a fraction of the genetic lesions that are responsible for cancer development have been identified. The hope is that continued improvements in genomic techniques, providing ever-increasing resolution, will lead to the identification of additional genetic changes that can be exploited to design better therapeutic strategies.

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REFERENCES

1. Pedersen-Bjergaard J, Andersen MT, Andersen MK. Genetic pathways in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 2007;2007:392-7.
2. Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. Hematology Am Soc Hematol Educ Program 2007;2007:29-39.
3. Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recent progress. Blood 2006;107:4223-33.
4. Meyer S, Fergusson WD, Whetton AD, et al. Amplification and translocation of 3q26 with overexpression of EVI1 in Fanconi anemia-derived childhood acute myeloid leukemia with biallelic FANCD1/BRCA2 disruption. Genes Chromosomes Cancer 2007;46:359-72.
5. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer 2003;3:639-49.
6. Mitelman F, Johansson B, Mertens F. The impact of translocations and gene fusions on cancer causation. Nat Rev Cancer 2007;7:233-45.
7. Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37.
8. Rabbitts TH. Chromosomal translocations in human cancer. Nature 1994;372:143-9.
9. Rowley JD. The critical role of chromosome translocations in human leukemias. Annu Rev Genet 1998;32:495-519.
10. Meyerson M. Cancer: broken genes in solid tumours. Nature 2007;448:545-6.
11. Shaffer DR, Pandolfi PP. Breaking the rules of cancer. Nat Med 2006;12:14-5.
12. Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. J Natl Cancer Inst 1960;25:85-109.
13. Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
14. de Klein A, van Kessel AG, Grosveld G, et al. A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukaemia. Nature 1982;300:765-7.
15. Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grosveld G. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. Cell 1984;36:93-9.
16. Heisterkamp N, Stephenson JR, Groffen J, et al. Localization of the c-ab1 oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. Nature 1983;306:239-42.
17. Goldman JM, Melo JV. Chronic myeloid leukemia — advances in biology and new approaches to treatment. N Engl J Med 2003;349:1451-64.
18. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood 2005;105:2640-53.
19. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408-17.
20. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001;293:876-80.
21. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome–positive ALL. N Engl J Med 2006;354:2542-51.
22. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305:399-401.
23. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. N Engl J Med 2006;354:2531-41.

24. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005;7:129-41. [Erratum, Cancer Cell 2005;7:399.]
25. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172-87.
26. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med 2002;347:481-7.
27. David M, Cross NC, Burgstaller S, et al. Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. Blood 2007;109:61-4.
28. Lichter P, Ward DC. Is non-isotopic in situ hybridization finally coming of age? Nature 1990;345:93-4.
29. Baccarani M, Cilloni D, Rondoni M, et al. The efficacy of imatinib mesylate in patients with FIP1L1-PDGFRalpha-positive hypereosinophilic syndrome: results of a multicenter prospective study. Haematologica 2007;92:1173-9.
30. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the *PDGFRA* and *FIP1L1* genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 2003; 348:1201-14.
31. Graux C, Cools J, Melotte C, et al. Fusion of NUP214 to ABL1 on amplified episomes in T-cell acute lymphoblastic leukemia. Nat Genet 2004;36:1084-9.
32. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
33. Delattre O, Zucman J, Plougastel B, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature 1992; 359:162-5.
34. Sorensen PH, Lessnick SL, Lopez-Terrada D, Liu XF, Triche TJ, Denny CT. A second Ewing's sarcoma translocation, t(21;22), fuses the EWS gene to another ETS-family transcription factor, ERG. Nat Genet 1994;6:146-51.
35. Owen LA, Lessnick SL. Identification of target genes in their native cellular context: an analysis of EWS/FLI in Ewing's sarcoma. Cell Cycle 2006;5:2049-53.
36. Riggi N, Stamenkovic I. The biology of Ewing sarcoma. Cancer Lett 2007;254:1-10.
37. Darnell JE Jr. Transcription factors as targets for cancer therapy. Nat Rev Cancer 2002;2:740-9.
38. Mrózek K, Heerema NA, Bloomfield CD. Cytogenetics in acute leukemia. Blood Rev 2004;18:115-36.
39. Licht JD, Sternberg DW. The molecular pathology of acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 2005:137-42.
40. Sanz MA. Treatment of acute promyelocytic leukemia. Hematology Am Soc Hematol Educ Program 2006:147-55.
41. Scaglioni PP, Pandolfi PP. The theory of APL revisited. Curr Top Microbiol Immunol 2007;313:85-100.
42. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood 2008;111:2505-15.
43. Küppers R. Mechanisms of B-cell lymphoma pathogenesis. Nat Rev Cancer 2005;5:251-62.
44. O'Neil J, Look AT. Mechanisms of transcription factor deregulation in lymphoid cell transformation. Oncogene 2007; 26:6838-49.
45. Perner S, Demichelis F, Beroukhim R, et al. TMPRSS2:ERG fusion-associated deletions provide insight into the heterogeneity of prostate cancer. Cancer Res 2006; 66:8337-41.
46. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005;310:644-8.
47. Liu W, Ewing CM, Chang BL, et al. Multiple genomic alterations on 21q22 predict various TMPRSS2/ERG fusion transcripts in human prostate cancers. Genes Chromosomes Cancer 2007;46:972-80.
48. Helgeson BE, Tomlins SA, Shah N, et al. Characterization of TMPRSS2:ETV5 and SLC45A3:ETV5 gene fusions in prostate cancer. Cancer Res 2008;68:73-80.
49. Tomlins SA, Laxman B, Dhanasekaran SM, et al. Distinct classes of chromosomal rearrangements create oncogenic ETS gene fusions in prostate cancer. Nature 2007;448:595-9.
50. Tomlins SA, Mehra R, Rhodes DR, et al. TMPRSS2:ETV4 gene fusions define a third molecular subtype of prostate cancer. Cancer Res 2006;66:3396-400.
51. Demichelis F, Fall K, Perner S, et al. TMPRSS2:ERG gene fusion associated with lethal prostate cancer in a watchful waiting cohort. Oncogene 2007;26:4596-9. [Erratum, Oncogene 2007;26:5692.]
52. Laxman B, Morris DS, Yu J, et al. A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. Cancer Res 2008;68:645-9.
53. Nam RK, Sugar L, Yang W, et al. Expression of the TMPRSS2:ERG fusion gene predicts cancer recurrence after surgery for localised prostate cancer. Br J Cancer 2007;97:1690-5.
54. Perner S, Mosquera JM, Demichelis F, et al. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. Am J Surg Pathol 2007; 31:882-8.
55. Kim SY, Hahn WC. Cancer genomics: integrating form and function. Carcinogenesis 2007;28:1387-92.
56. Hudis CA. Trastuzumab — mechanism of action and use in clinical practice. N Engl J Med 2007;357:39-51.
57. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244:707-12.
58. Garraway LA, Widlund HR, Rubin MA, et al. Integrative genomic analyses identify MITF as a lineage survival oncogene amplified in malignant melanoma. Nature 2005;436:117-22.
59. Kim M, Gans JD, Nogueira C, et al. Comparative oncogenomics identifies NEDD9 as a melanoma metastasis gene. Cell 2006;125:1269-81.
60. Zender L, Spector MS, Xue W, et al. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. Cell 2006;125: 1253-67.
61. Chin K, DeVries S, Fridlyand J, et al. Genomic and transcriptional aberrations linked to breast cancer pathophysiologies. Cancer Cell 2006;10:529-41.
62. Yao J, Weremowicz S, Feng B, et al. Combined cDNA array comparative genomic hybridization and serial analysis of gene expression analysis of breast tumor progression. Cancer Res 2006;66: 4065-78.
63. Dutt A, Beroukhim R. Single nucleotide polymorphism array analysis of cancer. Curr Opin Oncol 2007;19:43-9.
64. Pinkel D, Albertson DG. Array comparative genomic hybridization and its applications in cancer. Nat Genet 2005; 37:Suppl:S11-S17.
65. Holst F, Stahl PR, Ruiz C, et al. Estrogen receptor alpha (ESR1) gene amplification is frequent in breast cancer. Nat Genet 2007;39:655-60.
66. Albertson D. Conflicting evidence on the frequency of ESR1 amplification in breast cancer. Nat Genet 2008;40:821-2.
67. Weir BA, Woo MS, Getz G, et al. Characterizing the cancer genome in lung adenocarcinoma. Nature 2007;450:893-8.
68. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169-81.
69. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316: 1039-43.
70. Sansal I, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. J Clin Oncol 2004;22: 2954-63.
71. Cloughesy TF, Yoshimoto K, Nghiemphu P, et al. Antitumor activity of rapamycin in a Phase I trial for patients with recurrent PTEN-deficient glioblastoma. PLoS Med 2008;5(1):e8.
72. Neshat MS, Mellinghoff IK, Tran C, et al. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc Natl Acad Sci U S A 2001;98:10314-9.
73. Yilmaz OH, Valdez R, Theisen BK, et al. Pten dependence distinguishes haematopoietic stem cells from leukae-

mia-initiating cells. Nature 2006;441:475-82.
74. Hinds PW, Weinberg RA. Tumor suppressor genes. Curr Opin Genet Dev 1994;4:135-41.
75. Knudson AG. Two genetic hits (more or less) to cancer. Nat Rev Cancer 2001;1:157-62.
76. Okawa ER, Gotoh T, Manne J, et al. Expression and sequence analysis of candidates for the 1p36.31 tumor suppressor gene deleted in neuroblastomas. Oncogene 2008;27:803-10.
77. Zabarovsky ER, Lerman MI, Minna JD. Tumor suppressor genes on chromosome 3p involved in the pathogenesis of lung and other cancers. Oncogene 2002;21:6915-35.
78. Curtiss NP, Bonifas JM, Lauchle JO, et al. Isolation and analysis of candidate myeloid tumor suppressor genes from a commonly deleted segment of 7q22. Genomics 2005;85:600-7.
79. Döhner K, Brown J, Hehmann U, et al. Molecular cytogenetic characterization of a critical region in bands 7q35-q36 commonly deleted in malignant myeloid disorders. Blood 1998;92:4031-5.
80. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910-6.
81. Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 2006;24:2707-14.
82. Westbrook TF, Martin ES, Schlabach MR, et al. A genetic screen for candidate tumor suppressors identifies REST. Cell 2005;121:837-48.
83. Mullighan CG, Goorha S, Radtke I, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 2007;446:758-64.
84. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008;453:110-4.
85. Fodde R, Smits R. Cancer biology: a matter of dosage. Science 2002;298:761-3.
86. Ebert BL, Pretz J, Bosco J, et al. Identification of RPS14 as a 5q- syndrome gene by RNA interference screen. Nature 2008;451:335-9.
87. Boultwood J, Fidler C, Strickson AJ, et al. Narrowing and genomic annotation of the commonly deleted region of the 5q- syndrome. Blood 2002;99:4638-41.
88. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456-65.
89. Rivera MN, Kim WJ, Wells J, et al. An X chromosome gene, WTX, is commonly inactivated in Wilms tumor. Science 2007;315:642-5.
90. Calin GA, Sevignani C, Dumitru CD, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A 2004;101:2999-3004.
91. Zhang L, Huang J, Yang N, et al. MicroRNAs exhibit high frequency genomic alterations in human cancer. Proc Natl Acad Sci U S A 2006;103:9136-41.
92. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A 2002;99:15524-9.
93. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci U S A 2005;102:13944-9. [Erratum, Proc Natl Acad Sci U S A 2006;103:2464.]