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 physiological 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...
could serve as the basis for new treatments.\textsuperscript{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 \textit{ABL1} to the NUP214 gene on band 9q34.1. This fusion occurs on episomes — extrachromosomal elements that are invisible by standard cytogenetic analysis.\textsuperscript{31} Constitutively activated tyrosine kinases also drive many types of epithelial cancers.\textsuperscript{25} Point mutation or genomic amplification of tyrosine kinase genes have been well documented as mechanisms underlying aberrant tyrosine kinase activity in epithelial tumors.\textsuperscript{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 \textit{EML4} and the gene encoding the ALK receptor tyrosine kinase.\textsuperscript{32}

\textbf{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 \textit{EWSR1} gene on band 22q12.2 to a gene encoding a member of the \textit{ETS} family of transcription factors, most frequently \textit{FLI1} on band 11q24.1-q24.3 (in approximately 85\% of patients) and \textit{ERG} on band 21q22.3 (in approximately 10\% of patients) (Fig. 3B).\textsuperscript{33,34} The resulting chimeric transcription factors retain the DNA-binding domain of the respective \textit{ETS} family member and possess, in the \textit{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 \textit{EWSR1-ETS}–mediated tumor growth.\textsuperscript{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.\textsuperscript{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.\textsuperscript{38} For example, the chimeric proteins resulting from fusion genes such as \textit{PML-RARA

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{chromosome1.png}
\caption{Structure of a Human Chromosome.}
\end{figure}

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.
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.

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.

**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; 07/25/08)
IGKC, 2p12; and IGLC1, 22q11.2) drives the constitutive expression of the gene encoding the MYC transcription factor on band 8q24.21 (Fig. 3D).

Chromosomal changes that cause overexpression of structurally normal genes occur in other cancers of B-cell or T-cell origin 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. 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>
<thead>
<tr>
<th>Table 2. Selected Examples of Chromosomal Imbalances,*</th>
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<tbody>
<tr>
<td><strong>Genetic Change†</strong></td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Genomic gains</strong></td>
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<tr>
<td>Unknown target genes</td>
</tr>
<tr>
<td>+1q</td>
</tr>
<tr>
<td>+7</td>
</tr>
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<td>+8</td>
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<td>+12</td>
</tr>
<tr>
<td>+12p</td>
</tr>
<tr>
<td>+17q</td>
</tr>
<tr>
<td>Known target genes</td>
</tr>
<tr>
<td>amp(1)(q32.1)</td>
</tr>
<tr>
<td>amp(2)(p24.1)</td>
</tr>
<tr>
<td>amp(3)(p14.2-p14.1)</td>
</tr>
<tr>
<td>dup(6)(q22-q23)</td>
</tr>
<tr>
<td>amp(6)(q25.1)</td>
</tr>
<tr>
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<td>+9p</td>
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<td>amp(13)(q12.3)</td>
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<td>amp(14)(q13)</td>
</tr>
<tr>
<td>amp(17)(q21.1)</td>
</tr>
<tr>
<td>amp(21)(q22.3)</td>
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</table>
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

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Table 2. (Continued.)

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

* 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.
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.65,66

Large-Scale Genomic Gains
Genomic gains commonly arise from chromosomal nonsyndisjunction 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) and hepatic carcinoma (YAP1 and BIRC2 on bands 11q13 and 11q22, respectively) 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

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increases signaling through the phosphoinositide-3-kinase–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 leukemia80; deletions of chromosomes 11q, 13q, and 17p in chronic lymphocytic leukemia;81 and the concurrent deletion of chromosomes 1p and 19q in anaplastic oligodendroglioma.82

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 common deletion 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-
nomic losses will reveal additional tumor-suppres-

sion is that the loss of specific microRNAs with tumor-suppressive activity may contribute to tu-
morigenesis. 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 and the subsequent discovery that MIRN15A and MIRN16-1 negatively regulate the expression of the antiapoptotic protein BCL2. 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 gen-

omic losses will reveal additional tumor-suppress-

or microRNAs.

SUMMARY

Cancer is caused by genetic alterations that dis-

rupt the normal balance among cell proliferation, survival, and differentiation. The examples de-

scribed here illustrate that many of these altera-

tions 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 conven-
tional cytogenetic methods or modern genomic techniques can detect. Therefore, the analysis of chromosomal abnormalities can be used to iden-
tify 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 ge-
nomic techniques, providing ever-increasing reso-
lution, will lead to the identification of additional genetic changes that can be exploited to design better therapeutic strategies.

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