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REVIEW

Chromosome aberrations in solid tumors

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Chromosome aberrations in human solid tumors are hallmarks of gene deregulation and genome instability. This review summarizes current knowledge regarding aberrations, discusses their functional importance, suggests mechanisms by which aberrations may form during cancer progression and provides examples of clinical advances that have come from studies of chromosome aberrations.

Human solid tumor genesis and progression are enabled by the aberrant function of genes that positively and negatively regulate aspects of cell proliferation, apoptosis, genome stability, angiogenesis, invasion and metastasis[1]. Discovery and functional assessment of these genes is essential for understanding the biology of cancer and for clinical applications, including identification of therapeutic targets, early cancer detection and improved prediction of cancer risk and disease course. Many different factors can result in variant gene function, including polymorphisms, changes in genome copy number and structure, point mutations and epigenetic modifications. Furthermore, the mechanisms by which gene functions are altered vary between tumors. For example, tumor suppressor genes may be inactivated in some tumors by methylation and in others by mutation or physical deletion. Likewise, oncogenes can be activated by mutation, structural rearrangement or amplification. Because chromosome aberrations are distinctive features of tumors that can be detected using both cytogenetic and molecular methods, we review here current knowledge regarding these aberrations in solid tumors and discuss how they arise and how assessment of recurrent chromosomal changes can be used to improve understanding of tumor development. In addition, we consider the utility of specific aberrations as markers for prediction of disease outcome or response to treatment and as identifiers of genes to target for therapy or prevention.

Chromosomal aberrations in tumors

Chromosome aberrations can be analyzed using an increasing number of efficient, large-scale genomic and molecular genetic technologies, such as analysis of chromosome banding (Mitelman Database of Chromosome Aberrations in Cancer), high-throughput analysis of loss of heterozygosity (LOH; ref. 2), comparative genomic hybridization (CGH; refs. 3–6), fluorescence *in situ* hybridization (FISH; refs. 7–10), restriction landmark genome scanning (RLGS; ref. 11) and representational difference analysis (RDA; ref. 12). Some of these techniques, including RLGS, analysis of LOH and RDA, detect allelic imbalance that occurs by somatic recombination[13–15] or copy number change, whereas others such as FISH and CGH are only sensitive to physical changes in genome structure or copy number. These analyses identify a broad range of chromosomal abnormalities in solid tumors, including altered ploidy, gain or loss of individual chromosomes or portions thereof and structural rearrangements (**Fig. 1**). The structural changes may involve equal exchange of material between two chromosome regions (balanced) or may be non-reciprocal, such that portions of the genome are lost or gained. Restricted regions of the genome may be amplified and the amplified sequences present in small acentric fragments (double minutes), incorporated into tumor chromosomes in nearly contiguous homogeneously staining regions (HSRs) or interspersed in the genome. Notably, individual HSRs or other sites of amplified DNA may include genomic DNA originating from multiple different regions[16].

Extensive catalogs of recurrent abnormalities in a wide range of solid tumors have been compiled from cytogenetic (Mitelman Database of Chromosome Aberrations in Cancer) and CGH[17] studies and are available online (see list of URLs at the end of the article). These analyses indicate that there is considerable variability in the degree to which tumor genomes are aberrant at the chromosomal level. Some tumors have few chromosomal aberrations whereas others may contain dozens. The aberration spectrum, which comprises the numbers and types of aberrations and the regions that are recurrently altered, differs in tumors that arise in different anatomical sites and in histologically distinct tumors that arise in the same anatomic location[18,19]. Tumor histology and aberration spectrum also vary with the genetic makeup of the affected individual. For example, tumors in individuals with hereditary non-polyposis colorectal cancer are more likely to occur in the right colon[20] and to have diploid genomes, whereas the genomes of sporadic colorectal cancers are most often aneuploid[21–25]. Similarly, hereditary *BRCA1* and *BRCA2* breast tumors develop by specific and distinct evolutionary paths, as their gene expression profiles[26] and genome aberration spectra differ from each other and from those in sporadic breast tumors[27,28].

Functional importance

There is wide agreement that recurrent genomic aberrations contain genes that are important for tumor development. The importance of recurrent aberrations involving gene dosage is particularly clear. In

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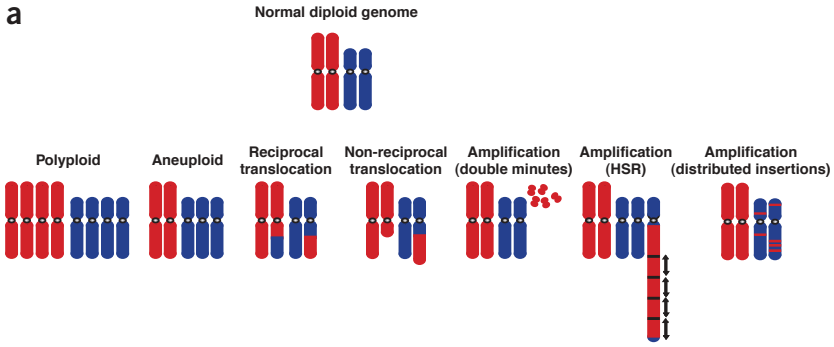

Technique	Detection						
Banding	+	+	+	+	+	+	–
SKY	+	+	+	+	+	+	–
CGH	–	+	–	+	+	+	+
LOH	–	+	–	+	+	+	+

Technique	Detection	
Banding	–	–
SKY	–	–
CGH	–	–
LOH	+	+

Figure 1 Schematic illustration of mechanisms by which chromosomal aberrations arise plus a summary of the ability of commonly applied technologies to detect the aberrations. (**a**) Aberrations that lead to aneuploidy. (**b**) Aberrations that leave the chromosome apparently intact.

many cases, these aberrations contain known oncogenes or tumor suppressor genes whose expression levels are altered by the genomic changes. Classic examples in solid tumors include amplification of established oncogenes, such as *ERBB2* (ref. 29), *MYC*[30] and *CCND1* (ref. 31). Amplification also has a key role in the development of drug resistance. Cultured cells selected for resistance to N-(phosphonacetyl)-L-aspartate[32,33] frequently amplify *CAD*, and development of resistance to methotrexate in cultured cells and in individuals with cancer is associated with amplification of *DHFR*[34]. Likewise, amplification of *BCR–ABL* is found in individuals resistant to STI571 (ref. 35), and amplification of *AR* occurs in prostate tumors that become resistant to endocrine therapy[36]. Other aberrations involve loss of specific regions of the genome. For example, deletions are important in the inactivation of tumor suppressor genes, such as *PTEN*[37] and *CDKN2A*[38], and in elimination of the remaining normal alleles in carriers of inherited mutations involving *RB1*, *BRCA1*, *BRCA2*, *PTPRJ* and *TP53* (refs. 39–42). Thus, it is reasonable to expect that additional genes important in cancer progression will be identified by assessment of other recurrently abnormal regions.

There are, of course, many more aberrations in solid tumors than the highly recurrent ones. The sheer number and variety has led to the assertion that many, if not most, aberrations are noise. But some evidence supports another view, that the seemingly random aberrations generated by failures in processes that normally maintain genome integrity are the result of selection during evolution of the tumor. This notion is consistent with the observation that relatively simple, stereotypical genomic changes arise in cells selected for drug resistance[43] and in tumors that arise in mouse models of cancer[44,45]. The stereotypical nature of the aberrations suggests that essentially all are the result of selection during tumor progression. Assessing the extent to which seemingly random elements of the human tumor aberration spectrum contribute or collaborate in the genesis or maintenance of the tumor will be an important area for future study.

Cytogenetic analyses have identified many structural chromosome changes in solid tumors (see the Mitelman Database of Chromosome Aberrations in Cancer), but relatively few are recurrent and have been shown to contribute to solid tumor development. In contrast, recurrent structural aberrations are frequent transforming events in sarcomas, leukemias and lymphomas[46] and include characteristic structural aberrations fusing *BCR* to *ABL* through the t(9;22) translocation in chronic myelogeneous leukemia[47] and *FOXO1A* to *PAX3* or to *PAX7* in rhabdomyosarcoma[48,49]. The paucity of important structural aberrations in solid tumors could be due to the difficulty of identifying and mapping structural rearrangements in these karyotypically complex genomes. But it also could be due to tissue-specific differences in mechanisms of aberration formation. For example, recombination is an essential step in the development of the hematopoietic progenitor cells in which leukemias arise, so there may be more opportunities for genes, such as *MYC*, *EVI1* and *CCND1*, to be activated by recombination-mediated translocations in leukemias, whereas they are activated more often by amplification and other means in solid tumors[30,50,51].

Identifying the important cancer-related genes in recurrent abnormalities is not always straightforward because the aberrations often contain multiple genes and more than one may be important. For example, regions that are highly amplified and contain known oncogenes, such as *ERBB2* and *CCND1*, typically span only a few megabases, and yet they may contain more than one gene that contributes to tumor progression. Examples include the growth factors *FGF19*, *FGF4*, *FGF3* and the actin-binding oncogene *EMS1* that are located in close proximity to *CCND1* and thus usually are amplified with *CCND1* (ref. 51). Likewise, the gene encoding growth factor receptor–bound protein, *GRB7*, is in close proximity to *ERBB2*. Altered expression of multiple genes included in an amplicon probably contribute to the tumor phenotype. For example, in a recent study of 14 breast cancer cell lines, >40% of highly amplified genes were overexpressed[52]. Moreover, because modulation of the expression of several of these genes influences aspects of tumorigenesis in model systems[53,54], it seems likely that some genomic rearrangements are selected because they alter the expression of multiple genes that coordinately promote tumor progression.

The functional consequences of recurrent gains or losses of single copies of regions of the genome, such as the losses of chromosomes 1p and 16q and gains of 1q and 3q that occur frequently in solid tumors, are even harder to establish, as the aberrations often extend over tens to hundreds of megabases and may affect hundreds to thousands of genes. The importance in cancer of the changes in gene expression that may be caused by these aberrations is supported by

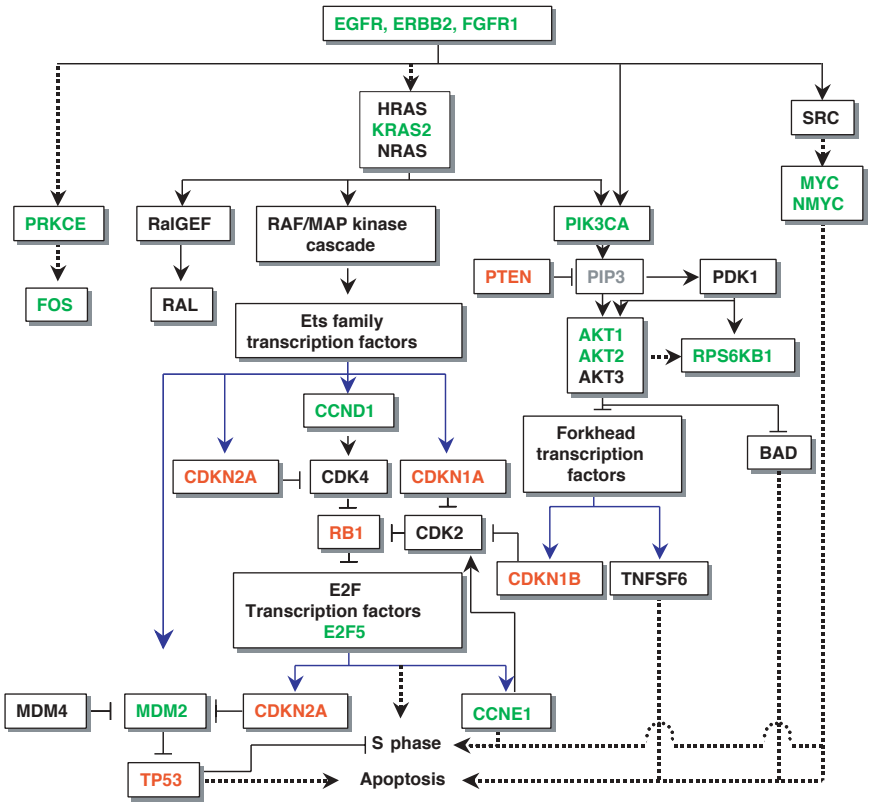

Figure 2 Schematic representation of receptor tyrosine kinase–mediated signaling. Factors found to be amplified in human tumors are indicated in green and those found to be frequently lost are indicated in red. Black lines indicate direct activation (arrowheads) or inhibition (bars), blue lines indicate transcriptional activation and dotted black lines indirect effects.

several reports linking haploinsufficiency of *CDKN1B*, *CDKN2A*, *MAD2L1*, *TCF3*, *BLM* and *TP53* to cancer[55–60], and moderately higher copy number of *PIK3CA* at 3q26 has been associated with activation of the phosphatidylinositol 3-kinase (PI3-kinase) pathway[61]. In addition, extra copies of individual chromosomes are associated with greater cancer risk[62] and poor clinical outcome in leukemias[63]. Thus, the modest changes in gene dosage caused by recurrent single copy-number aberrations probably do contribute to tumor development or progression. Technologies to scan genomes, transcriptomes and proteomes[6,64–68], optimized to allow reliable analyses of subtle changes in copy number or expression, should facilitate assessment of how the involved genes in these large regions exert their effects.

Additional support for the functional importance of chromosomal aberrations comes from the observation that many aberrations influence pathways that regulate cell growth or suppress apoptosis and that are known to contribute to tumor formation when deregulated. For example, **Figure 2** shows more than 20 genes involved in cellular signaling that have been found in regions of recurrent genomic abnormality and that may be deregulated by dosage changes. The rules governing how these pathways are deregulated are not yet clear but seem to vary according to tumor/tissue type and pathway. The RB pathway controlling entry into S phase provides an example. Inactivation of single genes in the pathway seems to be sufficient to alter cell cycle regulation in some tumors. In glioblastoma, for example, deletion of *RB1*, amplification of *CDK4* or inactivation of *CDKN2A* each seems to be sufficient to inactivate the pathway[69,70], whereas in melanoma, inactivation of *RB1*, mutation of *CDK4* or deletion of *CDKN2A* seem to be sufficient and perhaps mutually exclusive events[71]. In other cases, alterations in two RB pathway members may cooperate. For example, in head and neck cancers, deletion of *CDKN2A* and amplification of *CCND1* together are associated with a greater relative risk for recurrence, metastasis and death than either genetic alteration alone[72]. These observations are consistent with the effects of these genes on proliferation of cells in culture, where deregulation of both genes provides a greater growth advantage than either alone[73]. Analyses of data from large-scale measurements of genome copy number, gene expression and methylation that are now underway should refine our understanding of how the multiple aberrations interact.

Evolution of chromosomal aberrations in tumors

Tumor development typically proceeds through deregulation of gene expression such that the cells no longer respond to environmental cues and gain the capability to survive and proliferate inappropriately. Studies modeling tumor development in cultured cells or in rodents show that deregulation of only a few optimally chosen genes can initiate the process[74] and that the karyotypes of the resultant tumors can be near normal[75,76]. For example, overexpression of *MYC* and *BCL2L1* establish conditions that favor cell proliferation and decrease cell death and ultimately result in lesions that have the properties of human malignancies, including invasion, angiogenesis and metastasis. The genesis of human tumors, on the other hand, probably differs significantly from the relatively simple few-gene models that have been developed *in vitro* and in mice, because it is highly unlikely that altered expression of a few perfectly compensating genes occurs simultaneously by random mutation. More likely, human tumors evolve by accumulation of multiple alterations in small steps to tip the balance in favor of proliferation and tumor development.

Chromosomal change is one mechanism by which cells might tiptoe towards cancer. But the importance of chromosomal aberrations in tumor development varies substantially between tumors (**Fig. 3**). Some tumors undergo marked chromosome rearrangement[77] whereas others may evolve by mechanisms that result in little chromosomal change[25]. This variability may be due to differences in the mechanisms by which tumors are initiated, the manner in which genome stability is compromised[78], individual genotype or the particular epithelial cell type in which the tumor arises. The aberration spectrum also may be influenced by the stochastic nature of aberration formation. In those tumor types that are associated with chromosomal changes, the number of aberrations typically is small in premalignant, hyperproliferative lesions and substantially greater in more advanced lesions, supporting a role for acquisition of chromosomal aberrations in tumor progression. In breast cancer, for example, the aberration frequency is low in hyperplasia but often sharply higher in carcinoma *in situ*[79,80], whereas in colon cancer, genomic aberrations are present in high-grade dysplasias and adenomas[81] but

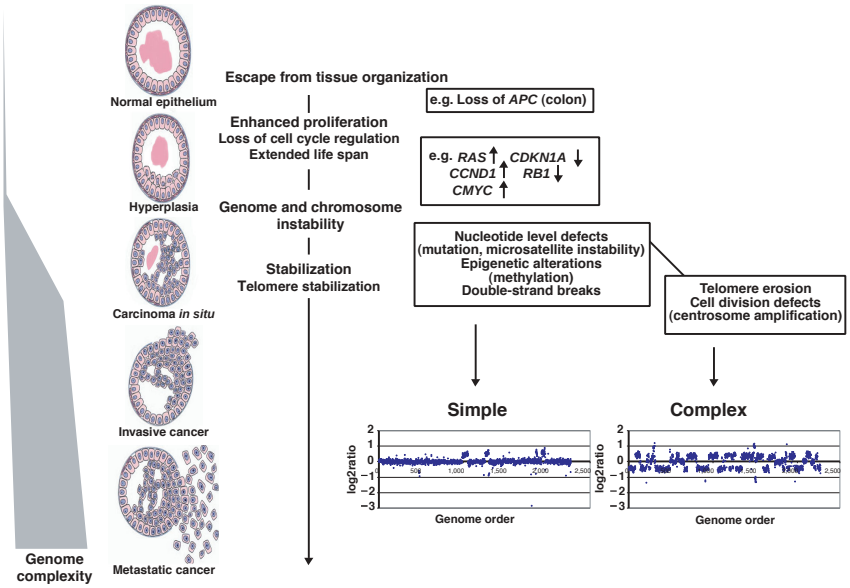

Figure 3 Schematic illustration of chromosomal evolution in human solid tumor progression. The stages of progression are arranged with the earlier lesions at the top. Cells may begin to proliferate excessively owing to loss of tissue architecture, abrogation of checkpoints and other factors. In general, relatively few aberrations occur before the development of *in situ* cancer. As indicated, a sharp increase in genome complexity (the number of independent chromosomal aberrations) in many (but not all) tumors coincides with the development of *in situ* disease. The types and range in aberration number varies markedly between tumors, probably owing to the specific failures in checkpoints or damage surveillance that are present, as illustrated by the whole-genome array CGH profiles of HCT116, a mismatch repair–defective cell line, and T47D, a mismatch repair–proficient cell line[64]. The copy number profiles of HCT116 and T47D are labeled as 'simple' and 'complex', respectively, to distinguish between tumor genomes with few or many copy number changes. The spectrum of aberrations in *in situ* lesions is similar to those found in more advanced malignancies. Thus, an early increase in chromosome aberration composition is followed by more modest chromosomal evolution.

significantly greater in number in carcinomas[81,82]. Notably, the chromosome aberration spectrum seems to stabilize in advanced cancers, as judged by the similarities between tumor genomes in within-individual comparisons of *in situ* and invasive lesions[83], primary and recurrent tumors[84] and primary and metastatic tumors[85]. These observations may indicate that the rate of chromosomal evolution has decreased in carcinomas, which could occur if some of the causes of chromosomal instability, to be discussed below, were removed. It is also possible, however, that tumors seem stable because advanced tumors have evolved a genotype that is optimized for growth and dissemination, making it less probable that additional lesions will confer further growth advantage. The remarkable karyotypic stability of established tumor cell lines in culture over many generations in many different laboratories supports this idea. These cells do show substantial cell-to-cell variability but the average genotype is stable[86]. Thus, selection is a strong force that eventually leads to an optimal, slowly evolving genotype.

Deregulation of processes responsible for maintaining genome integrity is probably important in aberration formation. Eukaryotic cells are subject to continual DNA damage from both extrinsic (*e.g.*, radiation, chemicals) and intrinsic (*e.g.*, reactive oxygen, stalling of DNA replication forks) sources. In fact, it has been estimated that as many as ten double-strand breaks occur per cell cycle[87], offering numerous opportunities for chromosomal rearrangements to occur. For this reason, elaborate systems have evolved to monitor genome integrity and coordinate cell cycle progression with DNA repair. More than 70 genes have been identified that have roles in DNA damage surveillance and repair[88]. These include genes involved in mismatch repair (*e.g.*, *MSH2*, *MLH1*), non-homologous end joining (*e.g.*, *XRCC5*, *LIG4*, *XRCC4*, *PRKDC*), homologous recombination (*e.g.*, *RAD51*, *BRCA1*, *BRCA2*) and signaling cascades responding to DNA damage (*e.g.*, *ATM*, *ATR*, *CHEK1*, *CHEK2*, *TP53*, *BRCA1*, *BRCA2*, *BLM* and *NBS1*; refs. 89–94). Different aberration spectra are associated with failures in the various systems. For example, abrogation of the function of *MSH2* or *MLH1*, genes involved in mismatch repair, result in tumors with few chromosomal aberrations but considerable microsatellite alterations[21,22,24,25,95]. Defects in genes involved in the repair of DNA double-strand breaks may lead to chromosome aberrations, such as translocations or amplifications (**Fig. 1**), and may be associated with high levels of chromosomal abnormality as observed in tumors arising in individuals or mouse models carrying mutations in *BRCA1* (refs. 27,96).

Chromosome gains or losses also may be expected when genes involved in chromosome segregation or cytokinesis are deregulated[78,97–102]. Aberrant centrosome behavior, termed centrosome amplification, is associated with mutation or loss of function of such genes as *TP53*, *STK15*, *RB1* and *BRCA1*. Centrosome amplification is characterized by the presence of abnormally large centrosomes, which may have >4 centrioles and altered functional properties, including hyperphosphorylation, increased microtubule nucleating capacity, abnormal centriole orientation and basal rather than apical position relative to the nucleus. It has been proposed as a primary source of genome instability in tumors, because it is associated with multipolar mitotic spindles, aneuploidy and unstable karyotypes. Thus, centrosome amplification may be a cause of both chromosomal instability and anaplasty in tumors.

Another form of chromosome instability may occur if tumors originate in somatic cells with inactive telomerase[103,104]. Continued proliferation of these cells will result in progressive telomere shortening. If surveillance mechanisms are sufficiently intact, cells will cease proliferating when telomeres reach a crucial short length[105–108]. Thus, telomere function provides a barrier to cancer development and may explain why benign lesions arrest[109,110]. If checkpoints are sufficiently compromised, however, then the chromosomes of cells with dysfunctional telomeres become susceptible to end-to-end fusions and subsequent breakage during cell division. The cells may undergo repeated rounds of aberrant cell division and genome reorganization. Most of the cells probably do not survive owing to abnormal and lethal chromosome rearrangements[108,111].

Rarely, however, a cell with proliferative capacity may re-establish telomere function by re-activating telomerase[110,112] or an alternative telomere maintenance mechanism (ALT; ref. 113). The extent of chromosome rearrangement that might occur during such 'telomere crisis' may be substantial but probably varies depending on the number of cell divisions in the presence of eroded telomeres, the functionality of other telomere maintenance genes and the types of damage surveillance systems that have been compromised.

A role for telomere dysfunction in the generation of chromosomal aberrations is supported by several observations. First, telomerase is active in most cancers but is less commonly observed to be active in hyperplastic lesions[114–116], and second, tumor telomeres are short relative to normal cells, consistent with a period of erosion[103,117]. Furthermore, the high level of genome rearrangement that occurs in some late-generation telomerase-knockout mice supports a role for telomere dysfunction in the generation of copy number aberrations[118]. On the other hand, a large number of tumors show few copy number changes. These tumors may have arisen in epithelial stem cells with active telomerase[110,119–121], telomere function may have been re-established before extensive genomic rearrangement, or they may be evolving by non-chromosomal mechanisms.

Clinical utility

Markers for chromosome aberrations that are important in solid tumor formation or progression facilitate cancer detection, prediction of clinical outcomes and response to therapy. In addition, identification of the genes involved in regions of recurrent aberration may be attractive targets for the development of new therapies.

Cancer detection. One promising approach to cancer detection uses FISH to detect cancer cells carrying specific numerical or structural aberrations. This approach has been used to assay exfoliated urothelial carcinoma cells in voided urine[122], lung cancer cells obtained using bronchoscopy[123] and cancer cells collected using fine needle aspiration[124]. FISH also has been used to detect rare disseminated cancer cells. For example, one study used CGH to detect specific genomic aberrations in primary tumors of acral melanoma and then used FISH to detect tumor cells carrying these aberrations in distant histologically normal regions to determine whether surgical margins were clear of tumor cells[109]. Extension of this approach to other tumor types promises to increase the accuracy of tumor margin assessment. FISH also has been used to detect circulating carcinoma cells in bone marrow and peripheral blood[125]. This assay eventually may be developed to identify individuals with metastatic disease who can then be offered systemic therapy. It is currently limited, however, by the low frequency of disseminated cancer cells and by an inability to distinguish between true metastatic cells and disseminated tumor cells that are not capable of proliferating at distant sites. In another approach, FISH has been used to determine if histologically ambiguous lesions, such as Spitz nevi, are benign by ascertaining if the lesions contain cells with aberrations characteristic of those that do not progress to cancer[126].

Analyses of microsatellite marker abnormalities also are proving useful for sensitive cancer detection. These PCR-based analyses screen for common tumor-associated genomic abnormalities in DNA collected from body fluids including feces, sputum, urine and serum. These analyses may target either exfoliated cells or free DNA. These assays have already been shown to be useful for early detection of cancers of the lung[127], colon[128], kidney[129], head and neck[130] and bladder[131]. Combining these assays with sensitive imaging technologies may prove especially valuable in detecting tumors sufficiently early that they can be curatively treated using surgery.

Prognosis and prediction. Numerous associations between genomic abnormalities and clinical behavior have been established. The association of amplification of *ERBB2* with reduced survival duration in individuals with breast cancer is a prototypical example[29]. Amplification of *MYCN* in metastatic neuroblastoma in infants is an even stronger negative prognostic indicator[132]. Large-scale genome profiling analyses have established other prognostic associations[133]. Typically, these result in stratification strategies for affected individuals that involve multiple genes. Although strategies based on detection of chromosome aberrations show promise, those based on gene expression currently seem more powerful. Microarray-based analyses of gene expression, for example, have shown the ability to identify individuals with breast cancer with short disease-free survival[68,134,135] or with metastatic disease[136]. These observations are interesting as they suggest that propensity to recur or metastasize is an intrinsic property of the primary tumor.

To date, prognostic associations have not been widely used clinically owing to the lack of alternative therapeutic strategies that can be applied to the different subgroups. But this situation is changing as gene-targeted therapeutics become available. Again, *ERBB2* serves as an example. *ERBB2* testing was of modest clinical interest until the development of Herceptin as a treatment for tumors that overexpress *ERBB2*. Now, analysis of *ERBB2* expression and amplification is an essential guide to treatment[137]. Regrettably, response to Herceptin and other targeted therapeutics can be predicted with only moderate accuracy, even when using the best assays for target expression. For example, only 30–40% of individuals who overexpress *ERBB2* will respond to Herceptin[138]. One possibility is that tumors may not respond because signaling pathways are deregulated at multiple points. The presence of activating aberrations downstream from *ERBB2* or in parallel to it supports this possibility (**Fig. 2**). Large-scale, therapy-linked molecular profiling efforts now underway may resolve such issues.

Target identification. Recurrent genomic aberrations are good indicators of genes that contribute causally to cancer genesis or progression and thus help to identify gene targets for therapy. For example, **Figure 2** illustrates several genes involved in receptor tyrosine kinase–mediated signaling that are recurrently abnormal, including *ERBB2*, *FGFR1*, and *EGFR*. The encoded receptors are targeted by monoclonal antibodies IMC-C225 and Herceptin and the small molecule tyrosine kinase inhibitors Iressa (ZD1839), Gleevec (STI571) and OSI-774 (refs. 139–141). Herceptin, a monoclonal antibody–based antagonist of *ERBB2*, is already approved for breast cancer[138], and Gleevec is approved for the treatment of chronic myeloid leukemia and shows activity against gastrointestinal stromal tumors[142]. Aberrations downstream in signaling pathways also suggest therapeutic opportunities. For example, amplification of *AKT2*, *RPS6KB1* and *PIK3CA*[61,143,144] and deletion of the negative regulator *PTEN*[37] all have been reported to activate PI3-kinase mediated signaling. These observations suggest the utility of PI3-kinase inhibitors, such as the rapamycin analog CCI-779 (ref. 145). These examples illustrate the potential of genome-based approaches to therapeutic target identification. It is important to note, however, that the absence of a genomic aberration does not indicate lack of response. As noted above, pathway activation may occur by genomic and non-genomic means, so, in general, recurrent genomic aberrations should be used to identify genes that are important therapeutic targets but not to estimate the fraction of tumors that might respond. In most cases, gene expression is expected to be a better indicator of response, but *ERBB2* may be an exception because, at least in breast cancer, overexpression is almost always caused by gene amplification[3].

The recurrent aberration maps assembled by Knuutila[17] and Mitelman suggest that many additional therapeutic targets remain to be discovered. Particular types of genome instability present in a tumor also may be of importance in planning treatment regimens. For example, cells with defects in mismatch repair are resistant to cisplatin[146]. Thus, identification of failures in particular mechanisms for maintenance of genome stability that might be present in tumors may provide both additional therapeutic targets and contraindications for others.

For the future

Identification of chromosomal abnormalities in solid tumors is becoming easier as genome-wide analysis technologies improve and as the genome sequence nears completion. Precise measurements of genome copy number analyses with sub-megabase resolution are now possible using array CGH with BAC arrays[45,64,147], and CGH with cDNA arrays allows analysis of individual genes[6,52], albeit at somewhat lower measurement precision. Improvements of these technologies in the near future will probably enable analyses that precisely interrogate essentially the entire genome for copy number changes. At the same time, multicolor FISH and optical mapping strategies based on microscopic analyses of individual DNA fibers digested with restriction enzymes[148] may facilitate identification of recurrent structural aberrations at high resolution and low cost. Application of these techniques will provide a detailed view of the spectrum of chromosome abnormalities that occur in human solid tumors. But chromosome aberrations are only one of several mechanisms by which genes are deregulated in solid tumors.

Other technologies are now emerging to provide equally comprehensive information about gene sequence, methylation, transcription, protein composition and protein phosphorylation status so that our knowledge of the changes that occur to enable tumor progression are more complete. High-throughput mutation detection strategies are now sufficiently advanced that it is possible to screen for gene mutations and polymorphisms in entire tumor genomes[149]. This approach has already led to identification of *BRAF* as a tumor suppressor gene that is important in malignant melanoma and other tumor types[149]. Transcription analyses of most known genes and a substantial number of splice variants are already possible using cDNA[150] or oligonucleotide[151] arrays, although high-throughput, quantitative PCR approaches[152] may challenge array-based methods when measurement precision is paramount. Serial analysis of gene expression (SAGE) provides unbiased, quantitative analyses of gene expression but at comparatively high cost[153]. Other nucleic acid analysis techniques are allowing efficient assessment of allele-specific expression[154], methylation status[65,149,155,156] and loss of heterozygosity (including homozygous deletions; ref. 37). Analyses of the cancer proteome using antibody arrays[157], immunostained cell lysate arrays[158] and mass spectrometry[159] are allowing efficient assessment of differences in protein composition of tumors. Furthermore, these analytical approaches can be combined, as for example, ChIP-on-chips in which the identity of genomic DNA recovered by chromatin immunoprecipitation is read using microarrays[160,161].

The amount of information becoming available on the biology and genetics of human tumors is staggering. The challenge now is to integrate these diverse data with information on clinical behavior, pathology, drug response, deregulated pathways and processes and with comparable information for the mouse. Several integration efforts are now underway, including databases that map diverse data onto the human genome and mouse sequences. The US National Cancer Institute Cancer Genome Anatomy Project is one example of effort aimed at integrating information on chromosome aberrations, molecular profiles, genome sequences, clinical behavior and clinical trials. Successful integration of information from these approaches should provide a more complete picture of the ways in which gene deregulation occurs in solid tumors, how multi-gene deregulation leads to specific tumor phenotypes and how this information can be used to improve cancer management[162].

URLs. The Mitelman Database of Chromosome Aberrations in Cancer is available at http://cgap.nci.nih.gov/Chromosomes/Mitelman. More information about the University of Helsinki's Laboratory of Cytomolecular Genetics is available at http://www.helsinki.fi/~lgl_www/CMG.html. More information about the US National Cancer Institute Cancer Genome Anatomy Project is available at http://cgap.nci.nih.gov/.

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