14

The Causes of Structural Aberrations

Ionizing radiation and many other exogenous or endogenous chromosome-breaking agents (*clastogens*) produce double-strand breaks (DSBs) in DNA. A DSB may be repaired, reuniting at its original breakpoint, or it may interact with another DSB to produce a chromosome rearrangement. According to the classical model of DSB resolution, the two broken ends of an unrepaired DSB separate from each other, whereas the exchange model postulates that the chromatin of the two broken ends is held together. Lucas and Sachs (1993) used three-color chromosome painting with FISH to examine interchanges involving chromosomes 1, 2, and 4. They found an excess of three-color triplets representing broken and rejoined chromosomes 1, 2, and 4, which is inconsistent with the exchange model and favors the classical model.

The sites of DSBs are referred to as "sticky ends" because of their tendency to rejoin with other broken ends. This is achieved by either of two mechanisms;

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both involve repair replication, which requires a DNA template. Meiotic repair (the basis of genetic recombination) uses a segment of the homologous chromosome as a template. Mitotic repair in G2 can use a segment of the sister chromatid as a template, which can lead to sister chromatid exchanges. The genetic makeup of a cell is not altered if a sister chromatid exchange (SCE) takes place at identical sites on the sister chromatids. However, if the breakpoints in the two chromatids are different, the resultant unequal (ectopic) SCE leads to a duplication of the intervening segment on one chromatid and its deletion from the other chromatid. At other stages of the cell cycle, mitotic repair can sometimes use an interspersed repeat as the source of a homologous sequence.

When there is no homologous sequence nearby, repair is achieved using short (1–5 bp) complementary sequences near the nonhomologous ends as a starting template. Using a new experimental approach, Liang et al. (1998) showed that DSBs are repaired 30–50% of the time by homologous processes (Fig. 14.1) and 50–70% of the time by nonhomologous processes. The latter generally result in small deletions, insertions, or larger rearrangements at the break site. The Ku70 and Ku86 proteins are required for nonhomologous DSB repair. They form a complex with DNA protein kinase, which is activated by binding to broken ends. This provides the signal that DNA damage has occurred, and initiates DSB repair by recruiting the additional proteins required for end joining.

The migration to sites of damage by some of these proteins, such as MRE11 and RAD50, has been observed by immunofluorescence with labeled antibodies to the proteins (Nelms et al., 1998). MRE11 has endonuclease activity (cutting at sites along the DNA) and also exonuclease activity (destroying DNA from a broken end). The latter is increased when MRE11 is in a complex with RAD50. These activities promote the joining of noncomplementary ends by making it possible to use 1 to 5-bp complementary sequences near broken ends (Paull and Gellert, 1998). Two other proteins that are an essential part of the DSB repair complex are nibrin (p95) and BRCA1 (Zhong et al., 1999). Nibrin is the product of the *Nijmegen breakage syndrome* (*NBS1*) gene (Chapter 24), and BRCA1 is the product of the *BRCA1* tumor suppressor gene (Chapter 28). XRCC2, a RAD51 homologue, is essential for efficient repair of DSBs by homologous, but not nonhomologous, recombination (Johnson et al., 1999).

Chromosomes may break at any stage of the cell cycle: G1, S, G2, mitosis, or meiosis. Different cell types and stages show different responses to chromosome-breaking agents. Most mutagens induce both chromosome breaks and gene mutations, changes that can lead to cancer (Chapter 26). Patients with ataxia telangiectasia are especially sensitive to the effects of ionizing

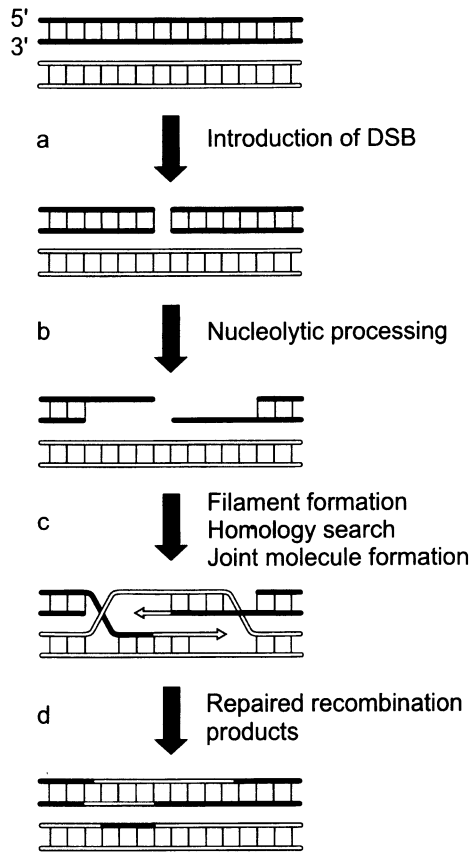

Figure 14.1. Double-strand break (DSB) repair model (modified and reprinted with permission from Kanaar and Hoeijmakers, Nature 391, p 335, copyright 1998, Macmillan Magazines Limited).

radiation and radiomimetic drugs (Chapter 24). This is important because the usual anticancer doses of these agents are lethal for them. Ionizing radiation and anticancer drugs can also cause secondary malignancies in any patient. Various aspects of chromosome breakage are reviewed in Mendelsohn and Albertini (1990).

Chromosome damage has been studied in various ways, such as by scoring dicentric bridges and acentric fragments in anaphase or by counting the micronuclei formed by damaged or lagging chromosomes (Prosser et al., 1988). The induction of breaks, and their healing, can be followed through interphase

by fusing the clastogen-treated cells with untreated cells blocked in metaphase; this induces prematurely condensed chromosomes (Chapter 23; Hittelman, 1990). An alternative approach allows the determination of chromosome abnormalities in both metaphase and interphase: chromosome painting by FISH with biotinylated chromosome-specific probes (Cremer et al., 1988). One can enhance the sensitivity of clastogen detection, and also get some idea of the effectiveness of DNA repair, by suppressing the repair process with high doses of caffeine (Puck et al., 1993). Alternatively, one can use cultured cells that have genetic defects in specific signaling and repair pathways (Wright et al., 1998; Chapter 24).

Two-break aberrations, such as quadriradials, dicentrics, and ring chromosomes, are easier to distinguish than one-break aberrations but are much rarer. Many studies on clastogens have used the more sensitive system of SCEs. Since bromodeoxyuridine (BrdU) itself induces SCEs, Pinkel et al. (1985) developed a method for measuring SCEs at very low levels of BrdU substitution in DNA, using a monoclonal antibody to BrdU. Alternatively, one can use a range of doses of BrdU, plot the SCE frequency against dosage, and extrapolate back to zero dosage to determine the spontaneous rate of SCEs or the rate due to particular exogenous agents. The spontaneous rate is about 2–5 per cell per two generations (the time required for the BrdU technique). In Bloom syndrome, the rate is 10–20 times as high (Chapter 24). The highest frequencies of SCEs are produced by bifunctional alkylating agents, such as methylmethane sulfonate, mitomycin C, and nitrogen mustards (Latt, 1981). UV light is also a powerful inducer, but ionizing radiation is not. A dose of X-rays that increases chromosome breakage 20-fold only doubles SCE frequency (Kato, 1977). SCEs frequently take place at common fragile sites (Glover and Stein, 1987; Chapter 20).

Exogenous Causes of Structural Aberrations

X-rays, γ-rays, α-particles, and other forms of ionizing radiation produce oxidants, such as superoxide, hydrogen peroxide, and the hydroxyl radical. These are powerful clastogens, while ultraviolet light is a much weaker clastogen. The effect of a given dose of radiation depends upon whether it is applied within a short time span (for example, an atomic bomb) or over a longer period,

which allows antioxidants to neutralize the oxidants more effectively and allows more time for DNA repair. Atomic bomb survivors of Hiroshima and Nagasaki showed a significantly higher incidence of chromosome abnormalities in their lymphocytes than did nonexposed controls. Those who received heavy doses of radiation still exhibited structural abnormalities almost 30 years later (Awa, 1974).

Chromosome breaks can also be induced by radiomimetic and other chemicals, including alkylating agents, purine and pyrimidine analogs, alkyl epoxides, aromatic amines, nitroso compounds, and heavy metals. Most chemicals induce breaks of the G2 type (present in only one chromatid), but they have to be present during the preceding S period. Some virus infections induce chromosome damage, which can vary from single chromosome and chromatid breaks to multiple rearrangements or total pulverization of the chromosome complement. This is found especially in lymphocytes of persons with an acute viral infection (Nichols, 1983). The "rogue" cells seen in a tiny fraction of cultured lymphocytes from different populations around the world may be another example of this. The occurrence of these cells is highly correlated with previous, and probably recent, exposure to the ubiquitous JC human polyoma virus (Neel et al., 1996).

The nature of the DNA damage, or lesion, depends on the clastogen involved. Ionizing radiation and bleomycin cause DNA strand breakage. Short-wave UV induces pyrimidine dimers. Alkylating agents induce base alkylation. Bifunctional alkylating agents, such as psoralen, or long-wave UV induces inter- and intrastrand crosslinks, and acriflavine, proflavin, or similar molecules intercalate (are inserted between base pairs) in the double helix. The lesions may undergo repair or misrepair by a wide range of DNA repair systems (Friedberg et al., 1995). The frequency of visible breaks decreases through G2, indicating that the majority of breaks that have not led to cell death eventually heal (Hittelman, 1990). Actinomycin D and cytosine arabinoside mimic the effect of adenovirus 12, which induces breaks at specific sites: the *RNU1*, *RNU2*, *PSU1*, and *RNS5* genes (Yu et al., 1998). Other fragile sites, hotspots for chromosome breakage, are discussed in Chapter 20. Ionizing radiation and most clastogenic chemicals do not increase the incidence of Robertsonian translocations. Some exogenous clastogens produce a highly nonrandom distribution of chromosome breaks, and the hotspots induced by different agents are not the same (Koskull and Aula, 1977). Chromosome breaks from any cause are usually seen in the gene-rich, GC-rich bands, but even in these regions they are unevenly distributed, with various sites emerging as hotspots. Certain

substances, such as mitomycin C, preferentially cause whole-arm interchanges (Hsu et al., 1978).

Spontaneous breaks and rearrangements of indeterminate origin occur infrequently in almost every cell culture and person, especially older people. The incidence of inducible structural changes also increases with age. The additive effects of known breaking agents, such as background cosmic rays and medical or occupational radiation, drugs, viral infections, or even high fevers, probably account for some of the increase in chromosome breakage at older ages. Progressive telomere shortening with age may also play a role (Chapter 4). Clastogenic oxidants are produced in great numbers during normal aerobic respiration and even more during phagocytosis. Most of these are destroyed by the various antioxidants found especially in fruit and vegetables, including vitamins C and E, but those remaining are a potential source of "spontaneous" chromosome breakage (Ames, 1989).

Endogenous Causes of Structural Aberrations

Genetic factors are a major cause of chromosome breaks. This is seen most clearly in the rare autosomal recessive chromosome breakage syndromes with their defective DNA repair enzymes (Chapter 24) and in the much more common somatic mutations in various mismatch repair genes, an important cause of tumor progression (Chapter 26). Inherent features of the genome, such as transposable elements (Chapter 7), interspersed repeats (Chapter 7), gene (including pseudogene) (Chapter 30) duplications, and fragile sites (Chapter 20), also predispose to structural aberrations. So does telomere shortening, from whatever cause. In the Thiberge-Weissenbach syndrome of scleroderma and telangiectasia, unbroken chromosome ends tend to unite with each other, leading to the formation of chains and rings, sometimes involving all the chromosomes (Dutrillaux et al., 1977). Could this be due to premature shutdown of the telomerase gene, which is normally active throughout early embryogenesis, leading to widespread premature telomere shortening and loss? Similar unstable terminal attachments of chromosomes have been described in cells of patients with ataxia telangiectasia (Chapter 24) and in some cancer cells (Fitzgerald and Morris, 1984; Chapter 26).

Transposable Elements and Other Interspersed Repeats

The presence of transposable elements in the genome is a major predisposing factor for structural aberrations, because they encode the enzymatic machinery (endonuclease and reverse transcriptase) needed for their own insertion. The inserted sequence may be stably integrated, becoming a permanent part of the genome. However, insertion of a DNA segment into a chromosome produces a region of nonhomology, whose presence may trigger a repair process that eliminates the insert or leads to chromosome breakage, a common occurrence with transposable elements. This may be how the introduction of telomeric TTAGGG repeats into an interstitial location destabilizes the site. Such introduction has been used for targeted disruption of a gene and even for the construction of an X-derived minichromosome less than 10 Mb in size (Farr et al., 1995).

Over millennia, hundreds of thousands of copies of a few short pieces of DNA (short and long interspersed elements, or SINEs and LINEs) have, by retrotransposition, been integrated into the genome and become fixed, that is, present at a specific site of integration on virtually all copies of the chromosome. The 300-bp *Alu* repeats make up 4–8% of the genome and occur, on average, about every 4 kb, with even closer spacing in the gene-rich R-bands. The longer LINE elements make up about 15% of the genome but are less common in the gene-rich regions than in the gene-poor ones. Most LINE elements are truncated and immobile. However, complete LINE-1 elements can still retrotranspose and cause insertion mutagenesis by disrupting a gene. Several examples involve the inactivation of tumor suppressor genes (Chapter 28), and others, to be described, have interesting features.

The extreme prevalence of interspersed repeated DNA sequences in the genome is a major cause of some structural aberrations, such as deletions, duplications, and inversions, because they predispose to unequal (ectopic or illegitimate) recombination (Fig. 14.2), a common cause of such events. These are usually interchromosomal, as seen in the 22q11.2 deletions responsible for the CATCH22 (Di George) syndrome and most of the 7q11.23 deletions in Williams-Beuren syndrome (Baumer et al., 1998). Sometimes they are intrachromosomal, as has been shown for the 15q11–q13 deletions in Prader-Willi syndrome (Carrozzo et al., 1997) and some of the 7q11.23 deletions in Williams-

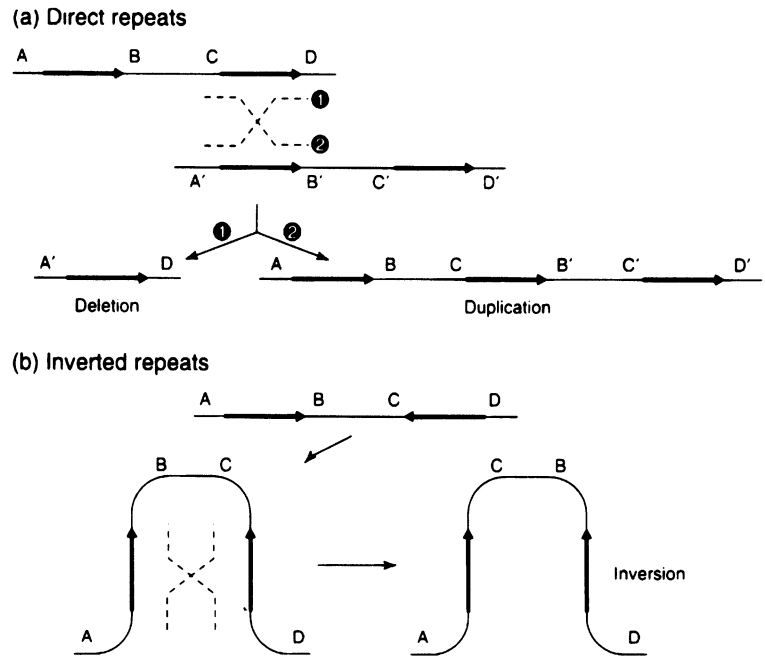

Figure 14.2. Genomic rearrangements resulting from ectopic recombination between repeated sequences (black arrows) on homologous chromosomes. Letters refer to unique sequences flanking the repeats, with A, B, C, and D on one of the homologues and A′, B′, C′, and D′ on the other (reprinted from Trends Genet vol 14, Lupski, Genome disorders: structural features of the genome can lead to DNA rearrangements and human disease traits, pp 417–422, copyright 1998, with permission of Elsevier Science).

Beuren syndrome. Mutations of the *TP53* gene can cause a 5 to 20-fold increase in the rate of spontaneous ectopic homologous recombination between intrachromosomal direct repeats (Bertrand et al., 1997). Deletions range from just a few base pairs to many megabases in size. The very short deletions, up to about 20 bp, are usually the result of ectopic recombination between short repeats, with the frequency of deletion greater if the repeat is longer or the distance between the repeats is shorter (Krawczak and Cooper, 1991). Unequal (ectopic) homologous recombination between neighboring LINE-1 elements led to a 7.6-kb deletion in the *phosphorylase kinase subunit B* (*PHKB*) gene and to resultant glycogen storage disease (Burwinkel and Kilimann, 1998). Several copies of the *MN7* gene are present near the common breakpoints seen in most indi-

viduals with either Prader–Willi or Angelman syndrome, suggesting that ectopic recombination among multiple copies of the *MN7* gene may be responsible for the 3 to 4-Mb deletion commonly seen in these individuals (Buiting et al., 1998).

Double-strand breaks in DNA appear to initiate such ectopic homologous exchange events. This has been shown for the inversion mutation that is so common in the mucopolysaccharidosis called Hunter syndrome. DSBs also lead to the duplication that causes the Charcot-Marie-Tooth type 1A (CMT1A) neurological disorder and to the deletion of the same region that causes hereditary neuropathy with liability to pressure palsies (HNPP) (Lagerstedt et al., 1997). The most intriguing aspect of this is that almost 80% of the breakpoints involved in the 1.5-Mb *CMT1A* duplication/*HNPP* deletion at 17p11.2–p12 occur within a 1.7-kb hotspot for recombination. Reiter et al. (1996) have proposed that the hotspot is due to the initiation of DSBs at a nearby *mariner* transposon-like element by a transposase enzyme. There are about 1000 *mariner* transposon-like elements in the human genome, and numerous other transposable elements, so this may be an extremely important cause of hotspots for chromosome breakage, analogous to the chromosome breakage Barbara McClintock's classic studies in maize showed accompanied the movement of transposable elements.

Interspersed Repeats as Hotspots for Double-Strand Breaks and Rearrangements

Interstitial deletions of short regions can arise by a process called *slipped mispairing* when there is homology (close sequence similarity) between the sequences flanking the region. This generates a single-stranded loop that is recognized by a DNA repair system and excised, producing the deletion (Krawczak and Cooper, 1991). In contrast to the wide distribution of these very short deletions, longer deletions tend to be clustered in particular areas of the genome and produce characteristic clinical syndromes. This may reflect embryonic lethality of deletions in other regions of the genome, but there is growing evidence that some sites are preferentially susceptible to the breaks leading to deletions and duplications, reflecting a particular origin. Thus, most patients with the Smith-Magenis syndrome (Chapter 15) have the same genetic markers deleted, cover-

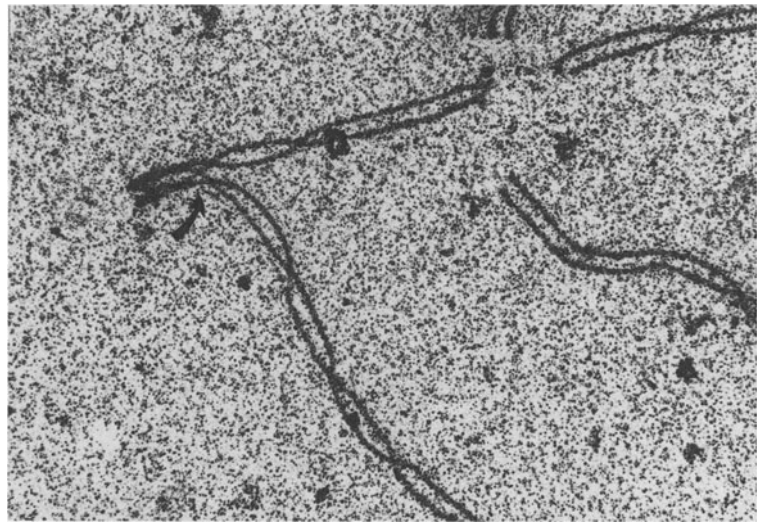

Figure 14.3. Visualization of a de novo translocation as an interchange (arrow) between two pachytene synaptonemal complexes (Speed and Chandley, 1990).

ing a 5-Mb region of 17p11.2. This region is flanked by low-copy repeats of a gene, and unequal homologous recombination between these repeats produces the common deletion (Chen et al., 1997).

Translocations and inversions also show breakpoint hotspots. Reciprocal translocations involving Xp and Yq are the result of rare recombination events between homologous sequences (Yen et al., 1991). That is also the case for some autosomal reciprocal translocations and for most Robertsonian translocations. Nearly 90% of translocations involving 11q also involve 22, with breakpoints at 11q23 and 22q11 (Fraccaro et al., 1980). This suggests that these two bands have a homologous sequence that tends to pair ectopically and lead to a translocation. Figure 14.3 shows the origin of a translocation during meiosis, perhaps generated by this mechanism. Other combinations that occur significantly more frequently than expected are t(9;22) and t(9;15).

Submicroscopic inversions are relatively common. The most abundant ones are very short, and the breakpoints are in inverted repeat sequences. These are fairly abundant throughout the genome. Inversions in the *factor 8C* (*hemophilia A*) gene in Xq28 provide an example. The underlying predisposing factor is the presence of a short region of homology in intron 22 of the gene and a region

in the opposite orientation 500 kb closer to the Xq telomere. Intrachromosomal homologous recombination between the mispaired regions produces an inversion of the specific segment. This inversion arises only in male meiosis, presumably because the presence of the correct pairing partners on the second X chromosome in females inhibits illegitimate pairing and recombination (Rossiter et al., 1994). Hunter syndrome, an X-linked mucopolysaccharidosis caused by a deficiency of iduronate sulfatase (IDS), is frequently the result of an inversion brought about by recombination between sequences in the *IDS* gene at Xq27.3–q28 and sequences in its closely linked pseudogene, *IDS-2*. All recombination appears to take place within a 1-kb region in which the sequence identity is over 98% (Lagerstedt et al., 1997).

The common inverted duplication of chromosome 15, inv dup(15) arises by illegitimate recombination between homologues by a U-type exchange rather than the usual X-type (Schreck et al., 1977). There is a common breakpoint in most of these cases (Wandstrat et al., 1998). This hotspot for breakage may account for the high frequency of this abnormality. Inverted duplications of the short arm of various chromosomes are well known, though not numerous except in the case of those leading to tiny supernumerary chromosomes like inv dup(15). Mono- and dicentric 8p duplications are produced by the same U-type exchange mechanism in maternal meioses (Floridia et al., 1996). Molecular studies have shown that inverted duplications of the short arms of chromosomes 3, 7, 8, and 9 are often accompanied by a deletion (deficiency) distal to the duplicated segment and frequently telomeric (Jenderny et al., 1998). The underlying mechanism for these duplication/deficiencies remains to be determined. Inverted duplications can arise by aberrant segregation in the carrier of an inversion involving an acrocentric chromosome in the rare case when one of the two breaks is in the short arm (Fig. 16.5; Trunca and Opitz, 1977). As a rule, crossing over in an inversion loop leads to duplication/deficiency chromosomes (Chapter 16).

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