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REVIEW ARTICLE

The Role of *Alu* Repeat Clusters as Mediators of Recurrent Chromosomal Aberrations in Tumors

Elena Kolomietz,[1] M. Stephen Meyn,[2] Ajay Pandita,[3] and Jeremy A. Squire[1]*

[1]Department of Laboratory Medicine and Pathobiology and Department of Medical Biophysics, University of Toronto, Princess Margaret Hospital and Ontario Cancer Institute, Toronto, Canada
[2]Genetics and Genomic Biology Program, Department of Molecular and Medical Genetics and Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Canada
[3]The Arthur and Sonia Labatt Brain Tumor Research Centre, The Hospital for Sick Children, Ontaria, Canada

There is increasing evidence for the involvement of repetitive DNA sequences as facilitators of some of the recurrent chromosomal rearrangements observed in human tumors. The high densities of repetitive DNA, such as *Alu* elements, at some chromosomal translocation breakpoint regions has led to the suggestion that these sequences could provide hot spots for homologous recombination, and could mediate the translocation process and elevate the likelihood of other types of chromosomal rearrangements taking place. The *Alu* core sequence itself has been suggested to promote DNA strand exchange and genomic rearrangement, and it has striking sequence similarity to χ (which has been shown to stimulate recBCD-mediated recombination in *Escherichia coli*). *Alu* repeats have been shown to be involved in the generation of many constitutional gene mutations in meiotic cells, attributed to unequal homologous recombination and consequent deletions and/or duplication events. It has recently been demonstrated that similar deletion events can take place in neoplasia because several types of leukemia-associated chromosomal rearrangements frequently have submicroscopic deletions immediately adjacent to the translocation breakpoint regions. Significantly, these types of deletions appear to be more likely to take place when the regions subject to rearrangement contain a high density of *Alu* repeats. With the completion of the Human Genome Project, it will soon be possible to create more comprehensive maps of the distribution and densities of repetitive sequences, such as *Alu,* throughout the genome. Such maps will offer unique insights into the relative distribution of cancer translocation breakpoints and the localization of clusters of repetitive DNA.

INTRODUCTION

Cytogenetic analysis of tumor cells has revealed that recurring chromosomal abnormalities such as translocations, deletions, and inversions are present in many tumors. In leukemias, lymphomas, and sarcomas, these specific chromosomal aberrations are frequently associated with specific morphologic subtypes. There have been a limited number of attempts to understand the underlying molecular mechanisms leading to the formation of the nonrandom genomic rearrangements that cause recurrent chromosomal aberrations in neoplasms. For hematologic neoplasms, several molecular mechanisms have been proposed to explain these chromosomal rearrangements, including illegitimate V(D)J recombination, homologous recombination mediated by *Alu* elements, translin activity, cleavage at sites of Z-DNA structure, topoisomerase II subunit exchange, repair of DNA breaks with nonhomologous chromosomes by nonhomologous end joining (NHEJ), and fragile sites. These mechanisms are not mutually exclusive, and it seems probable that the generation of a chromosomal rearrangement is the end result of a sequence of complex molecular interactions (Aplan, 1999). In this review, we discuss the evidence for the involvement of *Alu* elements and repetitive DNA in general as facilitators of chromosomal rearrangement.

SEQUENCE-DEPENDENT MECHANISMS OF REARRANGEMENT

Most of the proposed mechanisms that mediate nonrandom chromosomal rearrangements are sequence-dependent, and it has been suggested that various recombination-promoting sequences play a role. In lymphoid neoplasms, this view is supported by the presence of recombination signal sequence–heptamer/nonamer sequences characteristic of V(D)J recombination at the chromosome breakpoints (Finger et al., 1986; Tycko and Sklar, 1990).

A. Pandita is currently at Department of Experimental Pathology, Mayo Clinic, Rochester, MN.

*Correspondence to: Dr. Jeremy A. Squire, Ontario Cancer Institute (University Health Network), Division of Cellular and Molecular Biology, 610 University Avenue, Room 9-721, Toronto, Ontario, Canada M5G 2M9. E-mail: jeremy.squire@utoronto.ca

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The rearrangements observed in lymphoid neoplasms represent a specific dysregulation of the V(D)J recombinase system. However, a more general mechanism must be responsible for the translocations seen in other classes of neoplasms. It has been proposed that high densities of repetitive DNA such as *Alu* elements could provide hot spots for homologous recombination and mediate chromosomal translocation. More specific sequence elements have also been identified at translocation breakpoint regions. A number of chromosomal breakpoints have been mapped to the translin consensus sequence-binding site of the translin protein that is involved in DNA unwinding, which makes these regions more susceptible to nuclease cleavage (Aoki et al., 1995).

Other investigators have noticed some unusual DNA characteristics in the general regions of rearrangement. It has been reported that alternating purine and pyrimidine residues surround chromosomal breakpoints in a number of chromosomal translocations (Boehm et al., 1989; Adachi and Tsujimoto, 1990). These repeated tracts lead to the formation of a left-handed helical structure known as Z-DNA, altering chromatin organization and making the region involved more susceptible to DNA recombination events. Similarly, the presence of site-specific sequences that are uniquely susceptible to the DNA double-strand breaks induced by the treatment with topoisomerase II are thought to lead to translocations (Aplan et al., 1996; Strissel et al., 1998). More general properties of eukaryotic chromatin may also make some regions more susceptible to rearrangement. It has frequently been suggested that fragile sites predispose to intrachromosomal recombination (Glover and Stein, 1988) because cancer breakpoints are often associated with fragile sites (Le Beau and Rowley, 1984; Yunis and Soreng, 1984; Wenger, 1992). Interestingly, it has also been reported that the experimental induction of chromosomal fragile sites can lead to asynchronous replication timing and gene amplification (Debatisse et al., 1998). DNA, in general, is likely to be more susceptible to rearrangement when it is undergoing replication. It follows that the presence of repetitive sequences may, by virtue of high homology, be an additional destabilizing factor that could increase the likelihood of a rearrangement taking place within the developing replication fork (Flores-Rozas and Kolodner, 2000; Michel, 2000).

EFFECTS OF DNA DAMAGE

Various published studies have shown that DNA damage induces homologous recombination. DNA-damaging agents constantly challenge the integrity of chromosomes. To cope with DNA breakage, several different repair mechanisms have evolved, including NHEJ, homologous recombination (HR), and single-strand annealing. Chromosomal DNA breaks may be either single- or double-stranded. These breaks are thought to be potent inducers of recombination and can increase the frequency of HR (Rouet et al., 1994) and rearrangement between loci on nonhomologous chromosomes (Richardson et al., 1998) by 3 orders of magnitude or more. Double-stranded breaks (DSBs) can be generated by exposing cells to ionizing radiation or other types of DNA-damaging agents or from endogenous sources (e.g., nicks caused by free radicals arising from intermediary metabolism). In addition, some cellular processes such as DNA replication can also generate DSBs. It is also known that certain chromosomal regions, by the nature of DNA structure, are prone to spontaneous or induced breakage (Le Beau and Rowley, 1984; Yunis et al., 1987; Koduru and Chaganti, 1988). Certain sequences such as fragile sites are prone to DSBs, increasing the potential for recombination. It seems likely that genomic rearrangements could arise from misrepair of DSBs. Our basic knowledge of these processes in eukaryotes is derived largely by extension from studies in more amenable prokaryotic DNA-repair systems.

PROKARYOTIC SYSTEMS OF REPAIR INDICATE THE IMPORTANCE OF HOMOLOGOUS RECOMBINATION

In *Escherichia coli*, at least 25 different proteins are involved in HR. These include RecA, RecBCD, RecF, -G, -J, -N, and so forth; DNA polymerases; DNA topoisomerases; and DNA ligase. Many of these proteins have functional homologs in other bacteria, eukarya, and some phages. The RecA and RecBCD proteins interact with χ ("chi") motifs, crossover recombination hot spots that are short, orientation-dependent, strand-specific sequences implicated in Rec-mediated DNA recombination. The RecBCD enzyme is essential for 99% of recombination events occurring at DSBs in wild-type *Escherichia coli*, and for the repair of DNA damage and DSBs. RecBCD enzyme possesses a number of enzymatic activities, including single-stranded (ss) DNA exonuclease, ssDNA endonuclease, double-stranded (ds) DNA exonuclease, and DNA helicase activity. The RecBCD endonuclease unwinds dsDNA and simultaneously cleaves the ssDNA produced until it associates with a χ element (Kowalczykowski, 2000).

Upon recognition of the χ sequence, the 3′–5′ nuclease activity is attenuated, whereas its helicase activity remains unaltered (Dixon and Kowalczykowski, 1991). The χ sequence itself causes RecBCD to switch its functional interactions with DNA from exonuclease to recombinase activity. This change in functional state allows χ to act as a unique regulatory element by controlling the degradative function of RecBCD enzyme and, at the same time, enhancing its recombination function (Dixon and Kowalczykowski, 1993). The recombination-proficient RecBC enzyme (without a RecD subunit) has the ability to load RecA protein onto the χ-containing ssDNA sequences, ensuring incorporation of this ssDNA into a recombinationally proficient nucleoprotein complex (Kowalczykowski, 2000). This step is followed by the ssDNA searching, invading, and pairing with homologous DNA sequences and thus achieving DSB repair. The RecA protein is required for all HR in *Escherichia coli* and preferentially binds to χ sequences (Tracy and Kowalczykowski, 1996). The pairing of DNA by RecA protein is homology-dependent, suggesting that the basis of the elevated recombinational activity of χ and the increased genomic rearrangements between homologous DNA sequences may be greatly enhanced by local DNA-pairing activity. The specific mechanism by which RecA protein finds DNA sequences with homology is presently unclear, but it is thought to involve association primarily by passive diffusion (von Hippel and Berg, 1989).

HOMOLOGOUS RECOMBINATION IN EUKARYOTES

There is now growing evidence that HR has a similar function associated with repair in eukaryotes. Many of the proteins involved in the repair of DSBs by HR are encoded by the *RAD* genes, which were first identified in yeast (Flores-Rozas and Kolodner, 2000). It has been shown that the two critical steps in HR, the search for homologous DNA and the DNA strand-exchange process, comprise a remarkably phylogenetically conserved mechanism. Using the sequences of *E. coli* RecA and *S. cerevisiae* Rad51, *RAD51* homologs from higher eukaryotes were isolated (Shinohara et al., 1993), suggesting that the main process of HR is carried out by recA-like proteins in all living cells. RecA, Rad51p, and human RAD51 polymerize on DNA to form a nucleoprotein filament that searches for homologous DNA (Swagemakers et al., 1998). Further characterization of *RAD51* homologs, however, demonstrated that eukaryotic RAD51 has several functional differences from prokaryotic recA (Shinohara and Ogawa, 1999). First, eukaryotic cells contain multiple recA-like homologs. Second, Rad51 protein interacts with various proteins in the recombination reaction. At least seven RecA homologs have been identified in man, and, based on the recent genetic and biochemical analysis of the genes and proteins, these homologs can be divided into three subgroups: Rad51, Dmc1, and Rad55–57 (Shinohara and Ogawa, 1999). Whereas the Rad51 subfamily plays a pivotal role in both mitotic and meiotic recombination (Shinohara et al., 1992), the Dmc1 subfamily is a meiosis-specific homolog of Rad51/RecA (Bishop et al., 1992; Habu et al., 1996). The third group of proteins has an accessory role in the above two families in recombination and DNA repair.

For the enhancement of the Rad51 activities, other proteins, such as the replication protein-A RPA, Rad52, Rad54, Mre11, Rad50; the Nibrin/p95/NBS complex; and Rad55–57 are necessary for optimal formation of Rad51 filaments. It has been suggested that RPA stimulates Rad51-mediated DNA pairing and strand exchange by removal of secondary structures of the ssDNA for the formation of the continuous Rad51 filament (Shinohara and Ogawa, 1999). This RPA function is regulated by Rad52 (Sung, 1997; Benson et al., 1998; New et al., 1998), and it has been shown (Gasior et al., 1998) that Rad51 binding to DNA requires the preceding binding of Rad52 to DNA. Interaction of Rad51 with Rad54, a dsDNA-dependent ATPase of the Swi2/Snf2 superfamily (Petukhova et al., 1998; Swagemakers et al., 1998), is necessary for efficient Rad51-mediated pairing between homologous DNA molecules in vitro because Rad54 facilitates unwinding of a DNA duplex before its interaction with the ssDNA within the Rad51-DNA nucleoprotein filament. Rad51, similar to RecA, requires ssDNA as a substrate on which to form the nucleoprotein filament to carry out its homology search and strand-exchange activities. Exonucleolytic processing of the broken dsDNA is performed by the heterotrimeric complex composed of Mre11, Rad50, and Nibrin/p95/NBS [so called because it is mutated in the human chromosomal instability disorder Nijmegen breakage syndrome (NBS)]/p95 (Dolganov et al., 1996; Trujillo et al., 1998; Paull and Gellert, 1999).

One of the most distinctive features of a eukaryotic Rad51 protein is that the protein interacts with multiple proteins such as *BRCA1* and *BRCA2* gene products (Scully et al., 1997; Wong et al., 1997), ABL (Yuan et al., 1998; Chen et al., 1999), and TP53 (Sturzbecher et al., 1996; Buchhop et al.,

1997) proteins, suggesting that they work in the same DNA-repair pathway for keeping genome integrity.

Rad51 plays a central role in HR and DNA repair. Eukaryotes have evolved a variety of proteins that regulate the Rad51 functions positively and negatively (Shinohara and Ogawa, 1999). The precise functions of these proteins and their role in orchestrating the repair of DSBs are poorly understood and are currently the subject of extensive analyses. For reasons outlined below, we suggest that repetitive sequences may facilitate the process of HR in mammalian DNA, and that this may be instrumental in the process of chromosomal rearrangement.

INTERACTION OF HR AND NHEJ PATHWAYS OF DNA DOUBLE-STRAND REPAIR

To maintain the integrity of the genome and to prevent the formation of chromosomal rearrangements, fidelity of the repair of DSBs is crucial for each organism (Pastink et al., 2001). In eukaryotes, the repair of DSBs is carried out by two main pathways: the NHEJ and HR mechanisms, with single-strand annealing playing a relatively minor role. The fundamental difference between these pathways is their dependence on DNA homology and the concomitant accuracy of repair (Essers et al., 2000). In general, HR ensures accurate repair by using the undamaged sister chromatid as a template. However, homologous chromosomes or sequence repeats on nonhomologous chromosomes (such as repetitive *Alu* elements) can also serve as homologous repair templates, thereby increasing the risk of loss of heterozygosity by gene conversion or generating chromosomal rearrangements, respectively. Generally, nonmutagenic outcomes of homologous repair in mammalian cells can be explained by the preferred use of sister chromatids as repair templates (Kadyk and Hartwell, 1992; Johnson and Jasin, 2000), with the rate of recombination in mammals between sister chromatids (intrachromosomal recombination) in somatic cells being almost 5,000-fold higher than that which occurs between homologous chromosomes (interchromosomal recombination) (Shulman et al., 1995; Pastink et al., 2001).

In contrast to HR, NHEJ uses no or extremely limited sequence homology to rejoin ends in a manner that is intrinsically error-prone. At present, two multicomponent complexes of NHEJ pathways have been identified. The first is a DNA-dependent protein kinase complex (DNA-PK), containing three components: Ku 70, Ku 80, and the catalytic subunit of DNA-PK (DNA-PKcs). The second complex is composed of DNA Ligase IV and XRCC4 (for reviews, see Critchlow and Jackson, 1998; Featherstone and Jackson, 1999; Smith and Jackson, 1999). The Ku complex is composed of a heterodimer of Ku 70 and Ku 80, which binds to DNA ends and recruits DNA-PKcs to the DSB, activating its kinase function. It also facilitates ligation by Ligase IV/XRCC4 complex by aligning the ends (Ramsden and Gellert, 1998).

Both HR and NHEJ are important in preserving genomic integrity and preventing the formation of large chromosomal rearrangements and the concomitant risk of neoplasia (Hoeijmakers, 2001). It has been suggested that HR and NHEJ pathways of DNA DSB repair have overlapping roles in the maintenance of chromosomal integrity and each predominates in the different phases of the cell cycle, such that the HR pathway functions during late S–G_2 phase, whereas the NHEJ pathway is preferentially used during G_1–early S phase (Sonoda et al., 1998; Takata et al., 1998). Indeed, it would be selectively advantageous for cells to restrict HR to the G_2 phase of the cell cycle when the genome has duplicated and the sister chromatid can be used as a template (Pastink et al., 2001). On the other hand, HR in G_1 may be more mutational than NHEJ (Ferguson and Alt, 2001) because of gene conversion events. Convincing evidence has recently been presented that NHEJ and HR can interact in the repair of a single DSB and presumably reduce the risk of chromosomal rearrangements (Richardson and Jasin, 2000).

DENSITY, DISTRIBUTION, AND STRUCTURE OF *Alu* REPEATS

More than a third of the human genome consists of repetitive sequences that are ubiquitously interspersed with single-copy sequences throughout the genome. A survey of human interspersed repeats has been updated recently (Smit, 1999). Almost all of these interspersed repeats have arisen by retroposition of an RNA intermediate followed by insertion of the resulting cDNA into the genome. *Alu* elements are the most abundant class of interspersed repeat sequences. It has been estimated that there are more than one million copies of the *Alu* core element per haploid human genome (Smit, 1996). *Alu* elements comprise 5 to 10% of the human genome, occurring on the average once every 4 kb, although in practice certain regions are much more densely populated with these repeats (Smit, 1999). Originally detected by hybridization (Korenberg and Rykowski, 1988), *Alu* repeats have

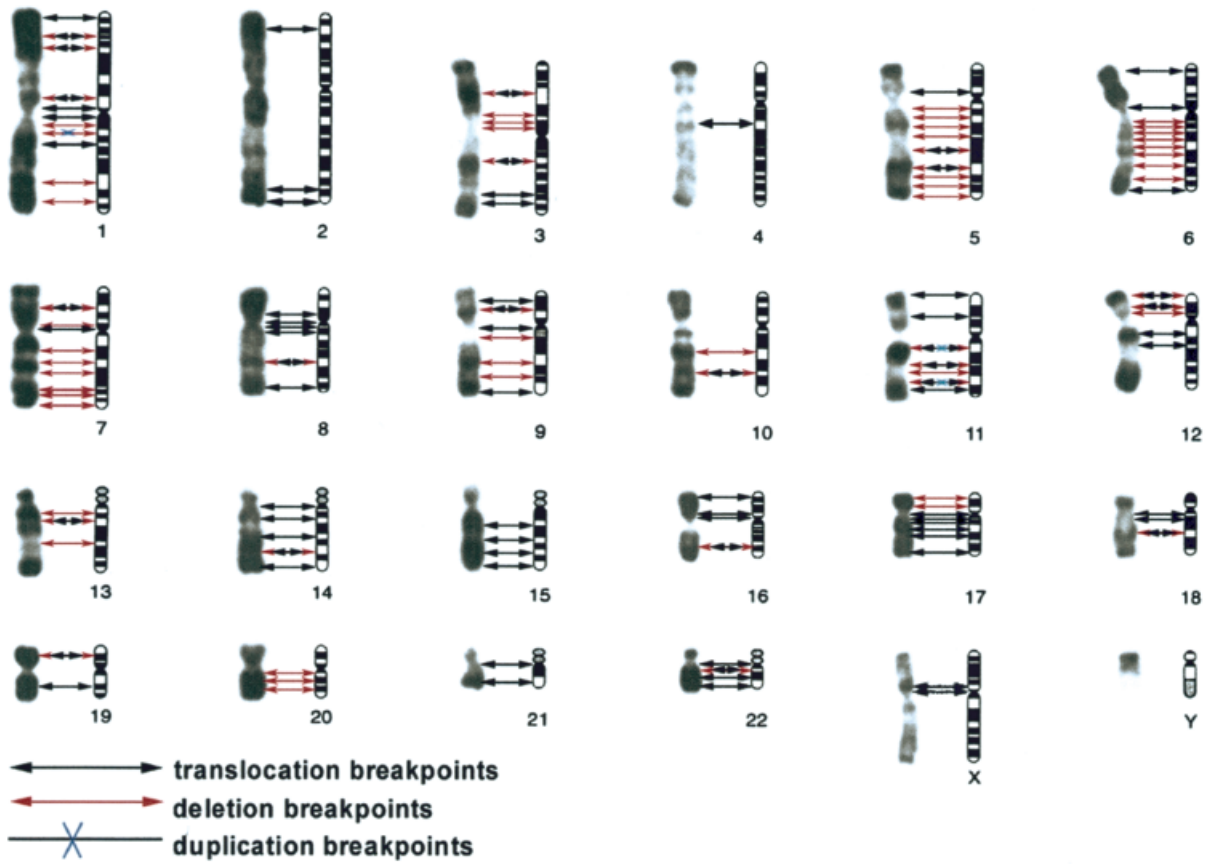

Figure 1. Positions of the cancer breakpoints of recurrent chromosome aberrations (summarized by the Cancer Genome Anatomy Project: http://www.ncbi.nlm.nih.gov/CCAP/mitelsum.cgi>) map to areas of accumulation of *Alu* repeats within R-bands.

been shown to hybridize preferentially to reverse bands (R-bands) of metaphase chromosomes (Holmquist, 1992; Craig and Bickmore, 1993). Differential distribution of *Alu* repeats in AT- and GC-rich DNA was later confirmed by computer-based analysis (Smit, 1996, 1999), demonstrating accumulation of *Alu* repeats within R-bands (see Fig. 1).

Human *Alu* repeats can be divided into subfamilies whose relative age can be estimated by analyzing sequence divergence away from the core functional sequence associated with transposition (Smit, 1996). The GC content of "young" *Alu* elements is ninefold greater than the average DNA content, and this class of recently transposed *Alu* elements also offers the potential for genomic methylation (Schmid, 1998). Individual *Alu* family members are highly homologous to each other, and 70–98% homologous to the *Alu* consensus sequence. The 282-bp consensus *Alu* structure has a precisely defined 5′ end, shared by most of its members, and is a divergent tandem dimer in which two monomers are separated by an A-rich region (Schmid, 1996). The two monomers are, in turn, homologous to 7SL RNA, an integral component of the signal recognition particle that governs the attachment of ribosomes to membranes of the endoplasmic reticulum. *Alu* elements contain internal A-box and B-box promoter elements for RNA polymerase III and are transcribed by Pol III in vitro.

Sequence analysis of the genomic DNA directly adjacent to translocation breakpoints has shown that the conserved 26-base pair (bp) *Alu* core sequence was present at or close (within 20–50 bp downstream or upstream) to the sites of recombination (Rudiger et al., 1995). These data strongly suggest that the *Alu* core sequence itself can promote DNA strand exchange and genomic rearrangement. The similarity of the *Alu* core sequence to χ, which has been shown to stimulate recBCD-mediated recombination in *E. coli,* is strongly supportive of a model in which the common 26-bp core sequence could, in some situations, provide the

binding site for the proteins catalyzing HR. In support of this hypothesis, it was shown recently that sequences closely homologous to translin DNA-binding sequences were identified within *Alu* consensus sequences (Jeffs et al., 1998). The translin protein associates with specific sequences and is involved in local DNA unwinding. Significantly, it has been shown that translin binding makes chromosomal regions more susceptible to both nuclease and recombinase activities (Aoki et al., 1995), making its close sequence identity within the *Alu* consensus provocative. In addition, the sequence similarity within the consensus sequence and the established prokaryotic model of recombination and DNA DSB repair provides further support to implicate a more direct role for *Alu* elements in chromosomal rearrangements. If such a hypothesis is correct, then it seems reasonable that *Alu* repeats are frequent sites for recombination, not only because of their abundance but also because they can serve as binding sites for RAD proteins. In such a model, *Alu* may thus both mediate and facilitate HR.

THE ROLE OF *Alu* ELEMENTS IN EVOLUTION

The ubiquitous presence of *Alu* elements in the primate genome and some of their sequence-dependent properties have led various investigators to ascribe functional roles for *Alu* elements in evolution: *Alu* repeats play a role as ubiquitous DNA methylation signals regulating gene expression and imprinting in the human genome (Schmid, 1996). The *Alu* transcript may activate protein translation by inhibiting dsRNA-regulated protein kinase PRK in response to cell stress, such as viral infection and heat shock (Chu et al., 1998; Schmid, 1998). It has been shown that retrotransposition of *Alu* elements can insert novel sequences within or near genes, leading to altered transcriptional expression (Norris et al., 1995; Vansant and Reynolds, 1995; Britten, 1996). Insertion can also lead to dysregulation of post-transcriptional events such as polyadenylation, splicing, and the creation of new exonic sequences (Schmid, 1996)

Alu REPEATS ARE IMPLICATED AS MEDIATORS OF GENOMIC REARRANGEMENT

When *Alu* elements are present on recombinant DNA constructs, they have been shown to increase the recombination frequency between vector DNA and the host genomic loci (Kato et al., 1986; Wallenburg et al., 1987; Kang et al., 1999), which is in keeping with this sequence element's role as a "hot spot" for recombination events. If unequal crossing over occurs between *Alu* elements intrachromosomally (in cis), it can result in deletion or duplication of intervening sequences. When *Alu*-mediated recombination occurs interchromosomally (in trans), it can lead to more complex chromosomal rearrangements such as translocations (Deininger and Batzer, 1999). Table 1 is an updated summary of the constitutive and acquired diseases in man that have been attributed to the presence of *Alu* repeats, insertions, or unequal recombination [the original summary was published by Labuda et al. (1995)].

Alu repeat–mediated mutations in meiotic cells, the result of unequal HR leading to deletions or duplications, bring about a number of constitutional diseases (Labuda, 1995; Harteveld et al., 1997; Tvrdik et al., 1998; Huie et al., 1999). Sixteen *Alu*-based insertion mutations were identified in the Human Genetic Mutation Database (Deininger and Batzer, 1999) (14,374 entries), suggesting that *Alu* repeats could contribute to 0.1% of human genetic diseases attributed to insertion alone (Janicic et al., 1995; Labuda, 1995; Rowe et al., 1995; Miki et al., 1996). *Alu* repeats have been implicated in the etiology of some recurrent somatic chromosome rearrangements such as the Philadelphia translocation in some cases of chronic myelogenous leukemia (CML) and complex *BCR/ABL1* rearrangements (Rogers, 1985; de Klein et al., 1986; Koduru et al., 1993; Chissoe et al., 1995; Zhang et al., 1995; Morris et al., 1996; Jeffs et al., 1998), Ph-positive ALL (Chen et al., 1989a,b; van der Feltz et al., 1989; Papadopoulos et al., 1990), as well as partial duplication of the *MLL* gene in acute myeloid leukemia, given that *Alu* repetitive sequences have been identified at or near the junction of translocation breakpoints (in most of the cases on both sides of the breakpoints).

Based on the preceding observations, it seems probable that *Alu* repeats may facilitate genomic rearrangement in some in vivo situations. The very high densities of *Alu* repeats at regions most frequently involved in chromosomal rearrangements are particularly compelling in this regard (Figs. 1 and 2).

MECHANISTIC IMPLICATIONS OF DELETIONS ASSOCIATED WITH RECURRENT CHROMOSOMAL REARRANGEMENTS

We and others have recently demonstrated that in about 10% of leukemia-associated chromosomal rearrangements, there are deletions immediately

TABLE 1. Disease-Causing Chromosomal Rearrangements Resulting From *Alu*-Mediated Recombination

Locus	Disease	References
	Disease-causing deletions due to *Alu*-mediated recombination	
BRCA1	Breast and ovarian cancer	Swensen et al., 1997; Montagna et al., 1999; Rohlfs et al., 2000
RB1	Glioma brain tumors	Rothberg et al., 1997
PDGFB	Meningioma	Smidt et al., 1990
MLH1	Familial colorectal cancer	Mauillon et al., 1996
MSH2 human DNA mismatch repair gene	Hereditary nonpolyposis colorectal cancer	Marshall et al., 1996
N-Acetylgalactosamine-6-sulfatase gene (*GALNS*)	Mucopolysaccharidosis type IVA	Hori et al., 1995
Alpha-galactosidase A	Fabry disease	Kornreich et al., 1990
α-Globin gene cluster	α-Thalassemia	Nicholls et al., 1987; Harteveld et al., 1997; Hattori et al., 1999
β-Globin gene cluster	δβ-Thalassemia, γδβ-thalassemia, HPFH2	Henthorn et al., 1990
C1 inhibitor gene	Hereditary angioedema	Stoppa-Lyonnet et al., 1990
Adenosine deaminase (*ADA*)	ADA-deficient SCID	Markert et al., 1988
Low-density lipoprotein receptor	Familial hypercholesterolemia	Hobbs et al., 1986; Lehrman et al., 1986
Platelet fibrinogen receptor	Glanzmann's thrombasthenia (GT)	Burk et al., 1991
Apolipoprotein B gene	Hypobetalipoproteinemia	Huang et al., 1989
von Willebrand factor A	von Willebrand disease	Bernardi et al., 1993; Ferreira et al., 1993; Zhang et al., 1994
FANCA	Fanconi anemia	Levran et al., 1998; Morgan et al., 1999
β-Hexosaminidase α-chain gene	Tay–Sachs disease	Myerowitz and Hogikyan, 1987
HEXB	Sandhoff	Neote et al., 1990
Hypoxanthine phosphoribosyltransferase	Lesch–Nyhan (LN)	Tvrdik et al., 1998
α-Glucosidase	Glycogen storage disease type II (GSDII)	Huie et al., 1999
	Disease-causing duplication due to *Alu*-mediated recombination	
C1 inhibitor gene	Hereditary angioedema	Stoppa-Lyonnet et al., 1990
Dystrophin	Duchenne muscular dystrophy	Hu et al., 1991
Lysyl hydroxylase	Ehlers–Danlos syndrome	Pousi et al., 1994
MLL dup(11)(q23)	Acute myeloid and lymphoid leukemia	Bernard et al., 1995; Schnittger et al., 1998; Strout et al., 1998; Wiedemann et al., 1999
	Disease-causing translocations due to *Alu*-mediated recombination	
t(11;22)	Ewing sarcoma	Obata et al., 1999
Ph translocation t(9;22)	CML, Ph-positive acute leukemias	de Klein et al., 1986; Chen et al., 1989a; Papadopoulos et al., 1990; Toth and Jurka, 1994; Chissoe et al., 1995; Martinelli et al., 2000
Variant Ph translocation	CML	Koduru et al., 1993; Morris et al., 1996; Jeffs et al., 1998
t(4;11)	Treatment-related acute lymphoblastic leukemia	Megonigal et al., 1997
t(14;18)	Follicular lymphomas (FLs)	Buchonnet et al., 2000
t(9;11)	De novo acute myeloid leukemia	Super et al., 1997
t(2;8)	Burkitt lymphoma cell line	Kato et al., 1991
t(14;19)	Chronic lymphocytic leukemia (CLL)	Ohno et al., 1993
t(11;22)c	der(22) syndrome	Hill et al., 2000*

*In contrast to the findings of Hill et al. (2000), it has been suggested recently that palindromic AT-rich repeats are responsible for the constitutional t(11;22) (Kurahashi et al., 2000)

adjacent to the breakpoint regions (Sinclair et al., 2000; Kolomietz et al., 2001). Our retrospective study of 250 cases of CML patients in chronic phase and blast crisis and 13 cases of Ph+ ALL patients indicated that 23 CML patients (9.2%) and 1 ALL patient (7.7%) exhibited a hybridization pattern consistent with deletion of two regions: proximal to the rearranged *ABL* gene and distal to the *BCR* gene on the der(9) chromosome. The observation that deletions are associated with both Ph-positive CML and ALL leukemias suggested that other leukemia-associated genomic rearrange-

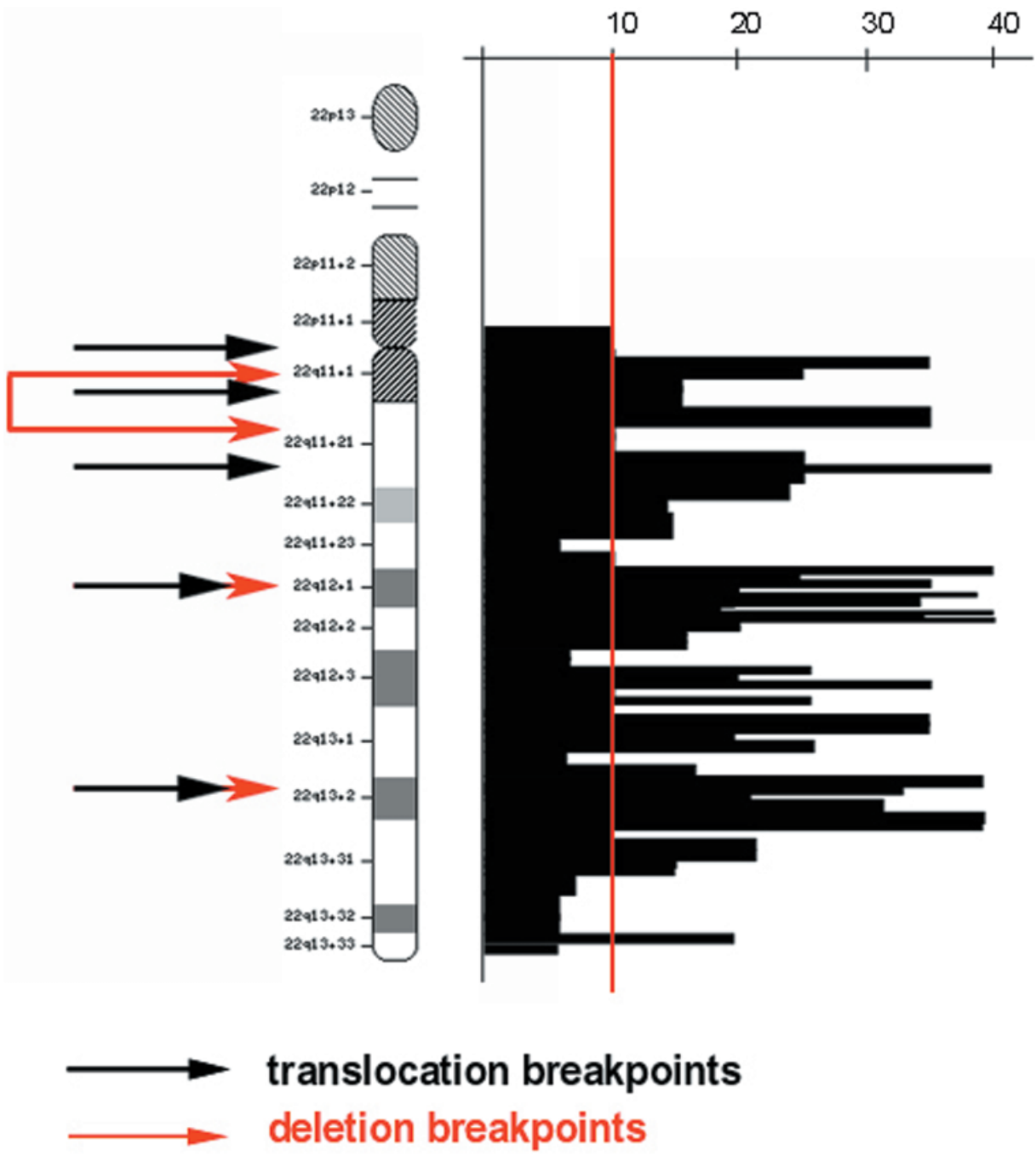

Figure 2. Results of computer-based DNA sequence analysis with the purpose of identification of repeat density for chromosome 22 were correlated with breakpoints of recurrent chromosomal aberrations to confirm genome-wide analysis based on in situ hybridization methods of mapping of *Alu* repeats (Korenberg and Rykowski, 1988). Cancer breakpoints on chromosome 22 map to the regions of clusters of *Alu* repeats with *Alu* density higher than 20%. In silico analysis of the complete genome sequence now permits detailed mapping of repetitive sequences throughout the human genome to improve our understanding of its role. A number of computer-aided programs such as Repeat Masker (http://ftp.genome.washington.edu/c/s.dll/RepeatMasker), Censor (http://www.girinst.org/), and BLAST (alu db) are widely used for the identification of repeats. These programs allow the user to identify and characterize different classes of repeats within a given genomic sequence and to map precisely their relative distributions and densities.

ments may also be subject to deletion in the break point flanking regions. This idea was confirmed by the detection of a deletion of the 3′ region of the *CBFB* gene in 20% ($n = 10$) of AML-M4 patients with inv(16)(p13q22). However, fluorescence in situ hybridization (FISH) analysis of two groups of

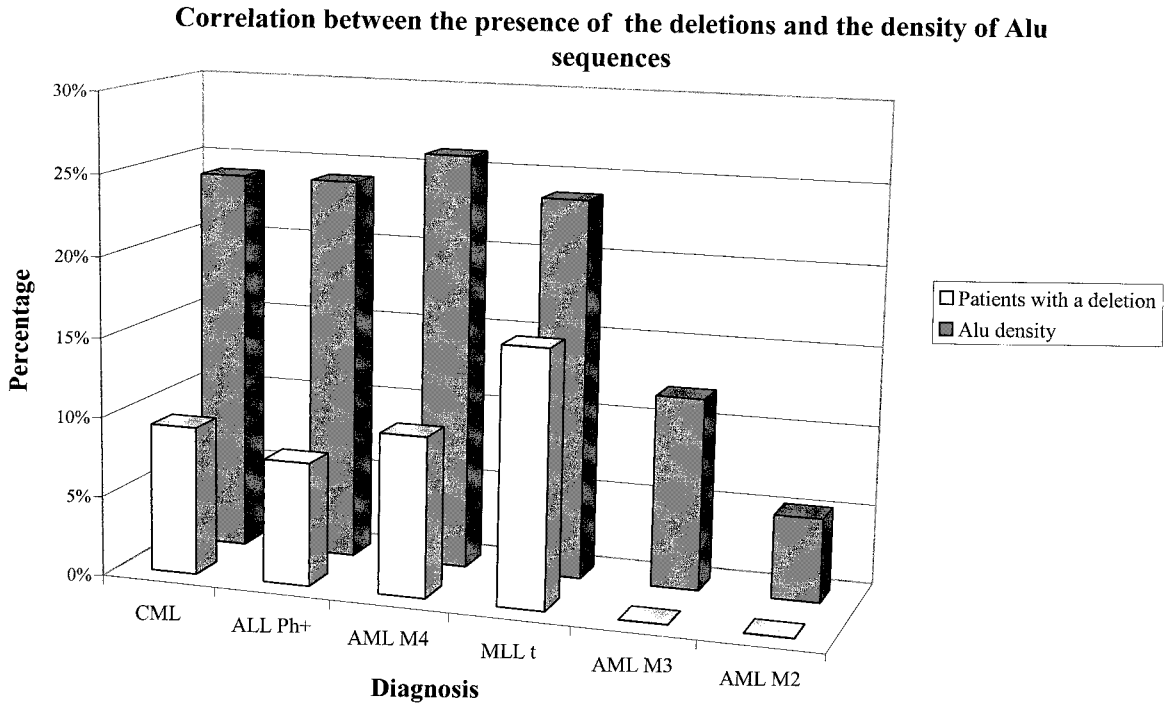

Figure 3. Correlation between the presence of the deletions associated with chromosomal rearrangements and the density of the *Alu* repeats in the genes involved in this rearrangement and their flanking regions.

patients, one with AML-M3 ($n = 30$) and the other with AML-M2 ($n = 14$), showed no deletions associated with the t(15;17)(q22;q11.2) and t(8;21)(q22;q22), respectively. In contrast, others (Godon et al., 2000) have identified deletions associated with the t(8;21). These findings suggest that such deletions are not disease-specific per se, but are more likely determined by the factors that influence the somatic process of chromosomal rearrangement itself. The fact that deletions are associated with different chromosomal rearrangements suggests that there might be a common mechanism for deletion formation, which is sequence-specific.

To investigate this possibility, DNA sequences of the genes involved in the chromosomal rearrangements and the adjacent flanking regions were submitted to the repeat identification programs Censor (http://www.girinst.org/Censor_Server-Data_Entry_Forms.html) and Repeat Masker (http://ftp.genome.washington.edu/cgi-bin/RepeatMasker), to identify the density of *Alu* repeats within the regions. Our findings suggest a strong association between the propensity to undergo deletion and an elevated density of *Alu* repeats in the chromosomal regions subject to rearrangement. A much higher density of *Alu* repeats was observed in the DNA sequences of the genes involved in the t(9;22) (*ABL* and *BCR*) and inv(16) (*CBFB* and *MYH11*) (over 20%) than in the genes involved in the t(15;17) (*PML* and *RARA*) (5–10%) (Fig. 3). It has recently been confirmed by computer-based analysis of *BCR* and *ABL* genes that *Alu* elements are the predominant repeat type in the *BCR* and *ABL1* genes and their distribution is nonrandom (Jeffs et al., 2001). This analysis revealed significant clusters of *Alu* elements at the 5′ end of both the *BCR* and the *ABL* genes. Sequence variation of *Alu* elements within subfamilies and a nucleotide difference between individuals have been reported (Chissoe et al., 1995). Concerning this observation, it has been suggested that certain sequence configurations of the *Alu* repeats are more susceptible to recombination than others. Although it remains unproved, it is tempting to speculate that in some individuals such nonrandom distribution may, in fact, play an important role in facilitating deletion formation, associated with chromosomal rearrangements, in neighboring genes that have close proximity to a flanking high density of *Alu* repeats.

Sinclair et al. (2000) have provided a detailed map of the regions that are subject to deletion on the derivative chromosomes 9 and 22. The dele-

tions vary in size from several hundred kilobases to 3–4 megabases and have variable breakpoints. It is well established that deletions of a few thousand base pairs will often be created by the action of endogenous endo- and exonucleases on the broken ends following DSBs (Szostak et al., 1983; Zucman-Rossi et al., 1998). Other studies have suggested that the small deletions ranging from several to 1,500 nucleotides that accompany translocation formation result from the base-pairing of fortuitously located direct repeats (microhomology spanned from 11–18 bp) flanking the DNA broken ends. When the direct repeats are joined together, the intervening DNA fragment will be deleted (Salganik and Dianov, 1992). *Alu* elements might serve as sites for unequal homologous crossing over, consequently scrambling their flanking genomic sequences (Schmid, 1996), leading to their deletion and/or amplification and possibly leading to the creation of the very large deletions reported by our group (Kolomietz et al., 2001) and others (Sinclair et al., 2000). Alternatively, *Alu* elements could partially recombine and hold chromosomal regions near each other. Consequently, rearrangements would be more likely to occur in the regions where *Alu* elements are present at higher densities (Chen et al., 1989a). Translocations may result from HR between *Alu* elements within the genomic sequences (Morris et al., 1996). However, it is more likely that the chance of rearrangement increases because attraction between *Alu* elements on nonhomologous chromosomes initially brings two genomic sites together. *Alu* sequences may base-pair following DSBs, either by means of physical juxtaposition arising from nonrandom nuclear compartmentalization (Neves et al., 1999) or by serving as substrates for HR after DSB. Rearrangement between homologous sequences could take place, even if there is no homology at the breakpoints because of spatial configuration of chromatin in nuclei (Neves et al., 1999).

It has also been suggested that transcriptionally active chromatin is more open in structure and thereby is prone to recombine more frequently than inactive chromatin (Datta and Jinks-Robertson, 1995). If this model is correct, then the open chromatin structure associated with the active transcription of the *BCR* and *ABL* genes in myeloid cells could increase the probability that these genes will associate, so that *Alu*-mediated recombination can then take place (Martinelli et al., 2000).

GENETIC INSTABILITY AND DISEASES WITH INCREASED FREQUENCY OF HOMOLOGOUS RECOMBINATION

The high density of *Alu* sequences in the human genome and the evidence that sequence-dependent HR is a major DNA repair pathway indicate that there must be a mechanism capable of regulating HR and preventing it from causing chromosomal instability. The fact that several genetic diseases have a DNA instability phenotype and a high frequency of carcinogenesis suggests a correlation between those mutations that result in a higher recombination frequency, genetic instability, and cancer predisposition (Bishop and Schiestl, 2000; Hoeijmakers, 2001). These diseases include ataxia telangiectasia (AT), Li–Fraumeni syndrome, Nijmegen breakage syndrome, Bloom syndrome (BS), Werner syndrome (WS), Fanconi anemia, Lynch syndromes I and II, Wiscott–Aldrich syndrome, and xeroderma pigmentosum.

BLM and *WRN*, the genes that are mutated in the cancer-prone disorders BS and WS, respectively, belong to the family of RecQ helicase homologs (Ellis et al., 1995; Yu et al., 1996; Enomoto, 2001). These two syndromes are characterized by a high degree of genomic instability, including chromosomal breaks, multiple large deletions, and translocations; moreover, cells derived from BS and WS patients show defects in DNA replication (Enomoto, 2001). It has become clear that DSBs could arise by active processing of stalled replication forks by a specific enzyme system (Michel et al., 1997; Flores-Rozas and Kolodner, 2000). HR plays an important role in the repair of stalled or broken replication forks, leading to the reinitiation of replication (Shinohara and Ogawa, 1995; Osman and Subramani, 1998; Flores-Rozas and Kolodner, 2000). Defects in the processing of stalled replication forks could lead to aberrant recombination events resulting in genetic instability (Enomoto, 2001). Recent studies on BLM, WRN, and the RecQ homolog of *S. cerevisiae*, Sgs1, indicate that these RecQ homologs function in a pathway from the DNA replication checkpoint to HR (Karow et al., 2000b). It has also been shown that BLM disrupts potentially recombinogenic molecules that arise at sites of stalled replication forks, suggesting a role of BLM in suppression of hyperrecombination (Karow et al., 2000a).

AT cells have an abnormally high rate of recombination and defective repair around the site of DNA strand breakage (Meyn, 1993; Luo et al., 1996). It is noteworthy that the knockout *Atm* gene

mouse model displays genetic instability and a significantly elevated frequency of intrachromosomal HR, resulting in deletion events (Bishop et al., 2000). These authors concluded that, because 25% of our genome consists of repeated elements, genomic instability attributed to an increased number of repeats and error-prone HR between such repeats might contribute to carcinogenesis in AT patients. The controlling role of *ATM* in HR-mediated repair (Morrison et al., 2000) provides the link between the recombinational repair machinery and the DNA damage checkpoint apparatus.

Mismatch repair (MMR) machinery is also known to suppress HR and microsatellite instability in both prokaryotic and eukaryotic cells (Rayssiguier et al., 1989; de Wind et al., 1995; Prolla, 1998; Harfe and Jinks-Robertson, 2000a). Recently, it was shown that MMR is also involved in suppression of other genomic instabilities such as gene amplification and chromosomal DNA integration (Lin et al., 2001).

HR involves the pairing of complementary single strands derived from two different duplexes, resulting in a heteroduplex DNA molecule. If the recombining duplexes are not identical in sequence, mismatches contained in the resulting heteroduplex are recognized and processed by MMR machinery, triggering one of two events: simple mismatch correction or complete abortion of the recombination event. In addition, MMR proteins are involved in the removal of the nonhomologous single-strand tails that are generated during the recombination processes (Harfe and Jinks-Robertson, 2000a).

The anti-recombination activity of the eukaryotic MMR machinery has been shown to inhibit recombination between diverged sequences both in mitosis and in meiosis (Harfe and Jinks-Robertson, 2000b). It has been demonstrated that a single mismatch is sufficient to inhibit recombination in an MMR-dependent manner, with additional mismatches having a cumulative negative effect on recombination rates (Datta et al., 1997; Chen and Jinks-Robertson, 1998). Moreover, sequence divergence not only inhibits HR but also reduces the efficiency of the single-strand annealing recombination pathway (Sugawara et al., 1997). Due to mismatch-triggered anti-recombination activity, eukaryotic MMR proteins inhibit ectopic interactions between divergent, repetitive DNA sequences such as *Alu* repeats during both mitosis and meiosis, and thereby promote genome stability by preventing deleterious genome rearrangements (Harfe and Jinks-Robertson, 2000a). Interestingly, mitotic recombination in yeast is more sensitive (in an MMR-dependent manner) to low levels of sequence divergence than is meiotic recombination (Chen and Jinks-Robertson, 1999), which may help reinforce the strong bias for sister chromatid vs. homologous chromosome interactions during mitosis. The observations made in yeast are likely to be relevant to the mismatch-associated regulation of recombination in higher eukaryotes (Harfe and Jinks-Robertson, 2000a,b).

Recent studies suggest that normal cells have stringent mechanisms for controlling HR, and that the altered expression of genes involved in DNA repair and DNA-damage sensing can lead to error-prone recombination and chromosomal rearrangement. Such changes may permit cells that have undergone these events to survive by escaping apoptosis (Richardson et al., 1998).

INFLUENCE OF CHROMATIN STRUCTURE AND REPEAT-MEDIATED REARRANGEMENT

Given the large number of repetitive elements in the human genome, it would be expected that recombination between these sequences could lead to gross genomic rearrangements, loss of genetic information, and general genetic instability (Bishop and Schiestl, 2000). Indeed, it has been shown that regions enriched in *Alu* repeat sequences do display an elevated incidence of genomic instability (Calabretta et al., 1982). However, cells must possess the mechanisms that limit and control the recombination process. The exquisite sensitivity of the HR process to any deviation away from perfect sequence homology allows cells to suppress recombination between divergent repetitive elements. The likelihood that HR will take place is a function of both the length of uninterrupted homology and the extent of perfect homology between two repetitive sequence elements (Wallenburg et al., 1987). Efficient recombination appears to require between 134 and 232 bp of uninterrupted homology; the recombination rate is primarily governed by the availability of contiguous uninterrupted homology (Waldman and Liskay, 1988).

It has also been shown that the frequency of *Alu*-mediated deletions in undamaged DNA is relatively low, with deletion rates in sperm of 3×10^{-7} and 7×10^{-7} and maximum frequencies of somatic mutation of less than 10^{-6} per cell (Hollies et al., 2001). It seems that chromosomal DNA breaks may be necessary inducers of recombination and therefore increase the frequency of HR (Rouet et al., 1994) and chromosomal rearrangements.

Chromatin structure creates an additional level of complexity for HR-mediated DSB repair. Both local and topologic differences in chromatin structure might strongly influence the likelihood of the search for homology being successful (Kanaar et al., 1998). Chromatin structure associated with *Alu* repeats may play a role in the suppression of HR between *Alu* repeats by complicating the process of homology search. Computational analysis of the organization of chromatin associated with *Alu* repeats indicated that the sequences are typically associated with rotationally positioned nucleosomes. Several lines of evidence (Englander et al., 1993; Englander and Howard, 1995) indicate that *Alu* repeat monomer elements are capable of setting the rotational phase of nucleosomes or nucleosome-like particles. Rotational positioning for *Alu* elements as a group reflects DNA sequence features intrinsic to these repeats (Englander and Howard, 1995). It is reasonable to speculate that nucleosome positioning over the *Alu* A-box promoter element might have a contributory role in suppression of HR between *Alu* repeats.

The relative position of different chromatin domains within the three-dimensional structure of the nucleus may play a role in mediating the recombination process. Nuclear topographic analysis of the relative position of the *ABL* and *BCR* genes has provided evidence for their close proximity in specific phases of the cell cycle (Koduru and Chaganti, 1988; Kozubek et al., 1997; Neves et al., 1999). Thus, physical juxtaposition arising from nonrandom nuclear compartmentalization may strongly facilitate the passive process of homology search and increase the chance of *Alu*-mediated rearrangement taking place.

Normal cells have mechanisms to control and suppress the occurrence of chromosomal rearrangements created by inappropriate repair of DSBs. Recent data suggest that the combination of factors—including the presence of sufficient uninterrupted homologous sequences of repeated elements, their topologic proximity resulting from the nuclear compartmentalization of the genes, and mutations in genes involved in DNA repair and DNA-damage sensing—may create the conditions in which error-prone recombination may lead to chromosomal rearrangement. *Alu* repeats play an important role in initiating such recurrent chromosomal rearrangements, in spite of their role in suppressing "promiscuous" recombination.

FUTURE DIRECTIONS

With the near completion of the entire Human Genome Sequence, it will be possible to create more detailed maps of the distribution and the density of repetitive sequences. Such maps will offer opportunities for better comparisons between the developing cancer breakpoints map [Breakpoint Map of Recurrent Chromosome Aberrations at CGAP (the Cancer Genome Anatomy Project) http://www.ncbi.nlm.nih.gov/CCAP/mitelsum.cg] and the localization of repetitive DNA. In this way, it will be possible to develop a better appreciation of the role of sequences such as *Alu* in chromosomal rearrangement and tumorigenesis. In addition, an improved understanding of the topologic architecture of chromatin and the role of both homologous and nonhomologous DNA repair will help to determine why chromosomal rearrangements preferentially take place in certain regions of the human genome.

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