Cell

Origin of Chromosomal Translocations in Lymphoid Cancer

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Aberrant fusions between heterologous chromosomes are among the most prevalent cytogenetic abnormalities found in cancer cells. Oncogenic chromosomal translocations provide cells with a proliferative or survival advantage. They may either initiate transformation or be acquired secondarily as a result of genomic instability. Here, we highlight recent advances toward understanding the origin of chromosomal translocations in incipient lymphoid cancers and how tumor-suppressive pathways normally limit the frequency of these aberrant recombination events. Deciphering the mechanisms that mediate chromosomal fusions will open new avenues for developing therapeutic strategies aimed at eliminating lesions that lead to the initiation, maintenance, and progression of cancer.

Introduction

Chromosomal translocations are the most common class of mutations found in hematological malignancies (Küppers, 2005). In addition, recurrent chromosomal fusions have been causally implicated in sarcomas and other solid tumors (Kumar-Sinha et al., 2008). There are a few common mechanisms by which translocations provide a proliferative or survival advantage to an incipient cancer cell. First, when *cis*-regulatory transcriptional elements from one gene are apposed to a proto-oncogene, this causes aberrant expression of the growth-promoting oncogene. For example, Burkitt's lymphoma carries a reciprocal translocation that results in fusion of the coding region of the *c-myc* proto-oncogene with the immunoglobulin heavy chain (IgH) (Jankovic et al., 2007), which places *c-myc* under the control of the 3′ regulatory elements of IgH (Gostissa et al., 2009). *c-myc* is thereby deregulated and promotes cellular transformation through its effects on the cell cycle, differentiation, and apoptosis. A second mechanism by which translocations may promote transformation involves the fusion of two genes to produce a chimeric protein with oncogenic activity. A prototypical example is the Philadelphia chromosome found in a subtype of acute lymphoblastic leukemia (Ph^+ ALL) and chronic myeloid leukemia (CML), in which the BCR-ABL fusion gene encodes a protein with deregulated kinase activity. BCR-ABL expression results in cytokine-independent growth, resistance to apoptosis, and genetic instability (Küppers, 2005). In addition to protein encoding genes, chromosomal translocations can also involve microRNA genes (Calin et al., 2004). Structural and functional alterations in these small noncoding RNAs have been detected in various cancers and may play a causal role in tumorigenesis (Calin and Croce, 2007; Robbiani et al., 2009).

Translocation requires (1) formation of paired double strand DNA breaks (DSBs) on separate chromosomes, (2) proximity of broken ends (at least transiently), and (3) joining of the heterologous DNA ends, as opposed to fusion in *cis* (Figure 1). Although many different cancers carry recurrent chromosome translocations (see http://www.sanger.ac.uk/genetics/CGP/Census/translocation.shtml), this review will focus on the etiol-

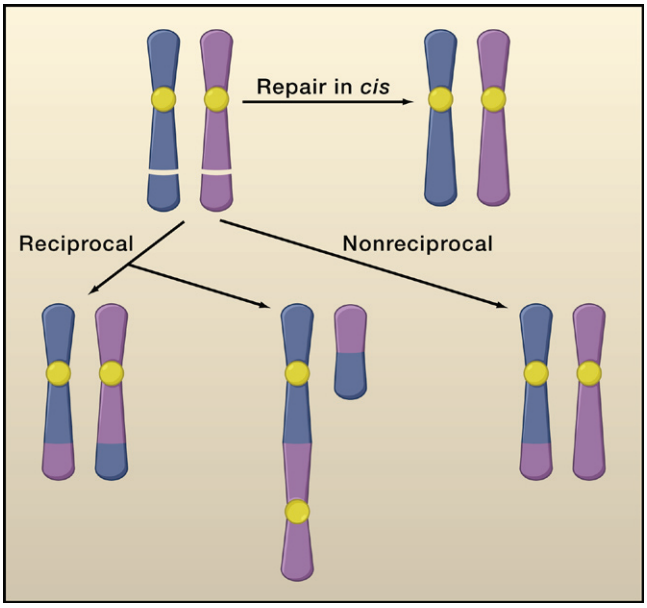

Figure 1. Misrepair of DNA Breaks Cause Chromosomal Translocations
Chromosomal translocations require formation of paired double-strand DNA breaks (DSBs) on different chromosomes. DSBs can be repaired in *cis* or can result in chromosomal translocation by rearrangement between nonhomologous chromosomes. Depending on the topology of the rearrangement, the translocation can be reciprocal (balanced or unbalanced) or nonreciprocal. The majority of translocations associated with cancer in human lymphoid tumors involve balanced chromosomal translocations, whereas epithelial cancers usually carry complex nonreciprocal translocations.

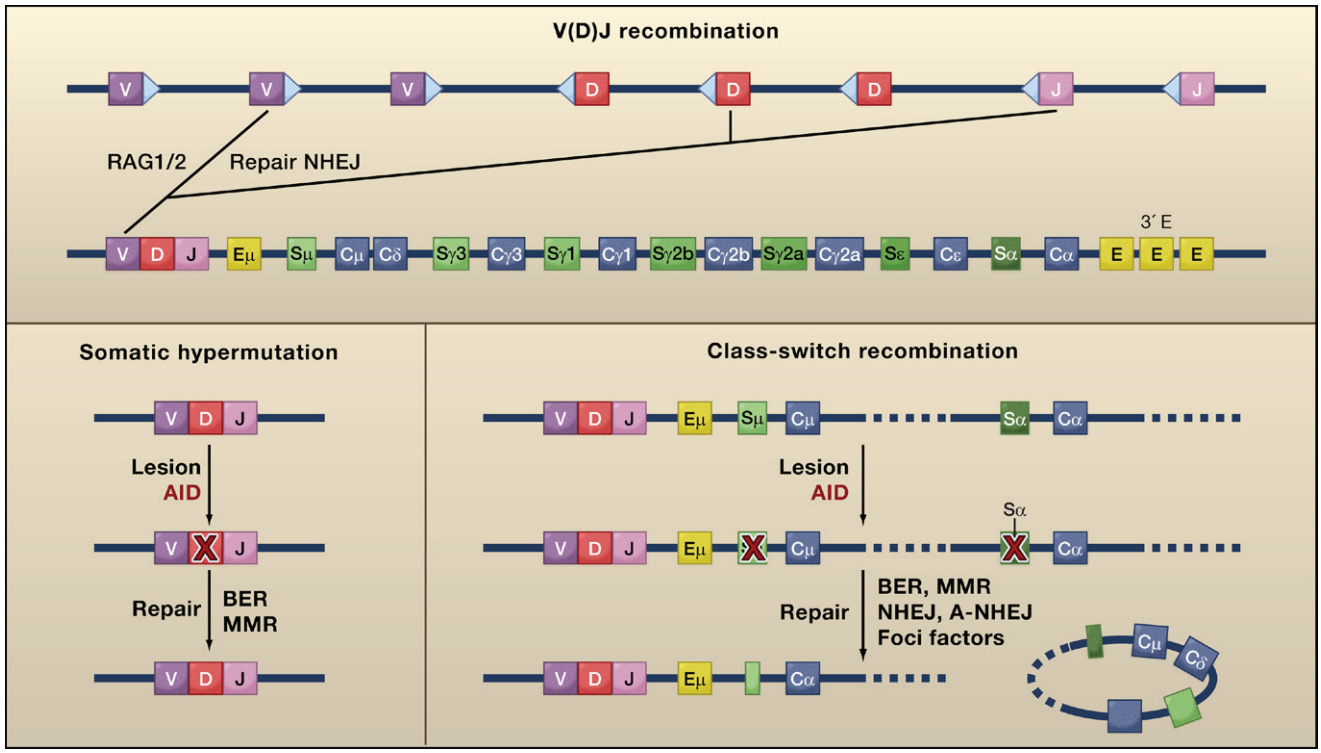

Figure 2. Antigen Diversification Reactions in Lymphocytes

Lymphocyte antigen receptor diversity is established in developing lymphocytes by V(D)J recombination. Recombinase-activating genes 1 and 2 (RAG1 and RAG2) are transesterases that introduce double-strand breaks (DSBs) at recombination signal sequences (shown in triangles) that flank V, D, and J gene segments. These DSBs are repaired by the NHEJ pathway. Mature B cells undergo two additional diversification reactions called somatic hypermutation and class-switch recombination. These two processes are initiated by AID, a single-strand DNA deaminase that mutates cytidine residues to uracyl. Cytdine deamination at V regions leads to somatic mutation whereas the same alteration in switch (S) regions causes class switching. AID generated mismatches in DNA are processed by base-exision repair (BER), mismatch repair (MMR), and error prone polymerases to generate mutations during somatic hypermutation. These lesions can also be converted to a DSB, an obligate intermediate during class-switch recombination. These DSBs are detected and processed by foci-forming factors, nonhomologous end joining (NHEJ), and alternative end joining (A-NHEJ). Accurate repair of DSBs by foci-forming factors and NHEJ is necessary to prevent chromosomal translocation. Most lymphoid cancers carry chromosomal translocations that involve RAG1/2 or AID target genes. Eμ, intronic enhancer; 3′E, 3′ enhancer.

ogy of translocations in lymphocytes as these are the most well characterized to date. We expect that most incipient cancer cells will share the basic mechanisms involved in the development of and protection against chromosomal translocations.

Chromosomal Translocations in Context

Approximately 95% of all lymphomas are of B cell origin (Küppers, 2005). These cancers are heterogeneous, involving all B cell developmental stages: from early B cells in acute lymphoblastic leukemia (ALL) to mature B cells in Burkitt's lymphoma and plasma cells in multiple myeloma. Despite their disparate origins, many of these cancers carry balanced chromosomal translocations that involve immunoglobulin (Ig) genes and oncogenic partner genes (Figure 1); in rarer cases, translocations can be nonreciprocal or join two non-*Ig* genes (Küppers, 2005).

Why are B cells particularly susceptible to transformation by chromosome translocation? This issue has been the subject of much debate, beginning immediately after these abnormal cytological features were discovered. A great deal of the discussion has focused on antigen receptor gene diversification during V(D)J recombination, somatic hypermutation (SHM) and class switch recombination (CSR), as all three require programmed DNA damage (Figure 2). The notion that antibody gene diversification reactions initiate translocations was strongly bolstered when the first lymphoid cancer associated translocation was characterized as a fusion between *c-myc* and the switch region of the *IgH* locus, suggesting that *c-myc/IgH* translocations arise as a byproduct of aberrant *Ig* class switching (Jankovic et al., 2007). In the ensuing years, many additional translocations have been documented in lymphoid cancers, and in most though not all cases, at least one of the partner chromosomes was an *Ig* variable or switch region. Translocations involving two non-*Ig* genes are interesting exceptions to the rule; however, this group of translocations may also be products of "off target" genome destabilization by the Ig V(D)J recombinase, recombinase-activating gene 1/2 (RAG1/2), and/or activation induced cytidine deaminase (AID) (Robbiani et al., 2009; Tsai et al., 2008) (see below).

Although less is known about translocations in other cell types, they appear to be frequent events in solid tumors, especially in sarcomas and prostate cancer (Lin et al., 2009; Mitelman et al., 2007; Tomlins et al., 2007). Recently published work suggests that in prostate cells interchromosomal interactions