Table 7-8 Selected Examples of Oncogenes Created by Translocations

Malignancy	Translocation	Affected Genes*
Chronic myelogenous leukemia (CML)	(9;22)(q34;q11)	*ABL* 9q34 *BCR* 22q11
Acute myeloid leukemia (AML)	(8;21)(q22;q22) (15;17)(q22;q21)	*AML* 8q22 *ETO* 21q22 *PML* 15q22 *RARA* 17q21
Burkitt lymphoma	(8;14)(q24;q32)	*MYC* 8q24 *IGH* 14q32
Mantle cell lymphoma	(11;14)(q13;q32)	*CCND1* 11q13 *IGH* 14q32
Follicular lymphoma	(14;18)(q32;q21)	*IGH* 14q32 *BCL2* 18q21
Ewing sarcoma	(11;22)(q24;q12)	*FLI1* 11q24 *EWSR1* 22q12
Prostatic adenocarcinoma	(7:21)(p22;q22) (17:21)(p21;q22)	*TMPRSS2* (21q22.3) *ETV1* (7p21.2) *ETV4* (17q21)

*Genes in bold type are involved in multiple rearrangements.

mechanisms of the translocation-mediated overexpression of *MYC* are variable, as are the precise breakpoints within the *MYC* gene. In most cases the translocation removes regulatory sequences of the *MYC* gene and replaces them with the control regions of the *IGH* gene, which is highly expressed in B-cells. The *MYC* coding sequences remain intact and the MYC protein is constitutively expressed at high levels. The almost invariable presence of *MYC* translocations in Burkitt lymphomas attests to the importance of *MYC* overactivity in the pathogenesis of this tumor.

There are many other examples of translocations involving oncogenes and antigen receptor loci in lymphoid tumors. For these (or any other) translocations to occur, double-stranded DNA breaks must occur simultaneously in at least two places in the genome and the free DNA ends must then be joined to create two new derivative chromosomes. In lymphoid cells most of these molecular misadventures are believed to occur during attempts at normal antigen receptor gene recombination (which occurs in both B- and T-cell progenitors) or class-switch recombination (which is confined to antigen-stimulated mature B cells). Not unexpectedly, tumors with translocations involving immunoglobulin genes are always of B-cell origin, and tumors with translocations involving T cell receptor genes are always of T-cell origin. The affected genes are diverse, but as with translocations involving *MYC*, the net effect is overexpression of some protein with oncogenic activity.

The *Philadelphia chromosome*, characteristic of CML and a subset of B-cell acute lymphoblastic leukemias (Chapter 13), provides the prototypic example of a chromosomal rearrangement that creates a fusion gene encoding a chimeric oncoprotein. In this instance, the two chromosome breaks lie within the *ABL* gene on chromosome 9 and within the *BCR* (*b*reakpoint *c*luster *r*egion) gene on chromosome 22 (Fig. 7-26). Non-homologous end-joining then leads to a reciprocal translocation that creates an oncogenic *BCR-ABL* fusion gene on the derivative chromosome 22 (the so-called Philadelphia chromosome).

The *BCR-ABL* fusion gene encodes a chimeric BCR-ABL protein with constitutive tyrosine kinase activity. Although the translocations are cytogenetically identical in CML and B-cell acute lymphoblastic leukemias (B-ALL), the structure of the resulting *BCR-ABL* fusion genes and proteins they encode usually differ slightly in these two tumors. Since the discovery of *BCR-ABL* in CML, many other fusion oncogenes encoding constitutively active tyrosine kinases have been described in a broad array of human cancers. Like BCR-ABL, these fusion proteins drive oncogenic signaling pathways and have sometimes proven to be targets of effective therapies.

Other oncogenic fusion genes encode nuclear factors that regulate transcription or chromatin structure. In contrast to overactive tyrosine kinases, less is generally known about how nuclear oncoproteins function. An exception with important clinical consequences is found in a form of leukemia called *acute promyelocytic leukemia* (APML). APML is virtually always associated with a reciprocal translocation between chromosomes 15 and 17 that produces a *PML-RARA* fusion gene (Fig. 7-41). How this fusion gene functions is now reasonably well understood.

- The fusion gene encodes a chimeric protein consisting of part of a protein called PML and part of the retinoic acid receptor-α (RARα). Normal RARα binds to DNA and activates transcription in the presence of retinoids. Among the RARα responsive genes are a number that are needed for the differentiation of myeloid progenitors into neutrophils.
- The PML-RARα oncoprotein has diminished affinity for retinoids, such that at physiologic levels retinoids do not bind to PML-RARα to any significant degree. In this "unliganded" state, it retains the capacity to bind DNA, but instead of activating transcription, it inhibits transcription through recruitment of transcriptional repressors. This interferes with the expression of genes that are needed for differentiation, leading to a "pile-up" of proliferating myeloid progenitors that replace normal bone marrow elements.
- When given in pharmacologic doses, all-trans retinoic acid binds to PML-RARα and causes a conformational change that results in the displacement of repressor complexes and the recruitment of different complexes that activate transcription. This exchange overcomes the block in gene expression, causing the neoplastic myeloid progenitors to differentiate into neutrophils and die, clearing the marrow over several days and allowing for recovery of normal hematopoiesis.

This highly effective therapy is the first example of *differentiation therapy*, in which immortal tumor cells are induced to differentiate into their mature progeny, which have limited life spans. It has also spurred efforts to develop drugs that target other nuclear oncoproteins, despite the inherent difficulty of the problem.

Deletions. Chromosomal deletions are another very prevalent structural abnormality in tumor cells. Deletion of specific regions of chromosomes is associated with the loss of particular tumor suppressor genes.

As we discussed earlier, deletions involving chromosome 13q14, the site of the *RB* gene, are associated with retinoblastoma, and deletion of the *VHL* tumor suppressor gene on chromosome 3p is a very common event in renal cell carcinomas. Ongoing sequencing of cancer cell genomes will undoubtedly reveal many more examples of deletions

www.PTools.ir