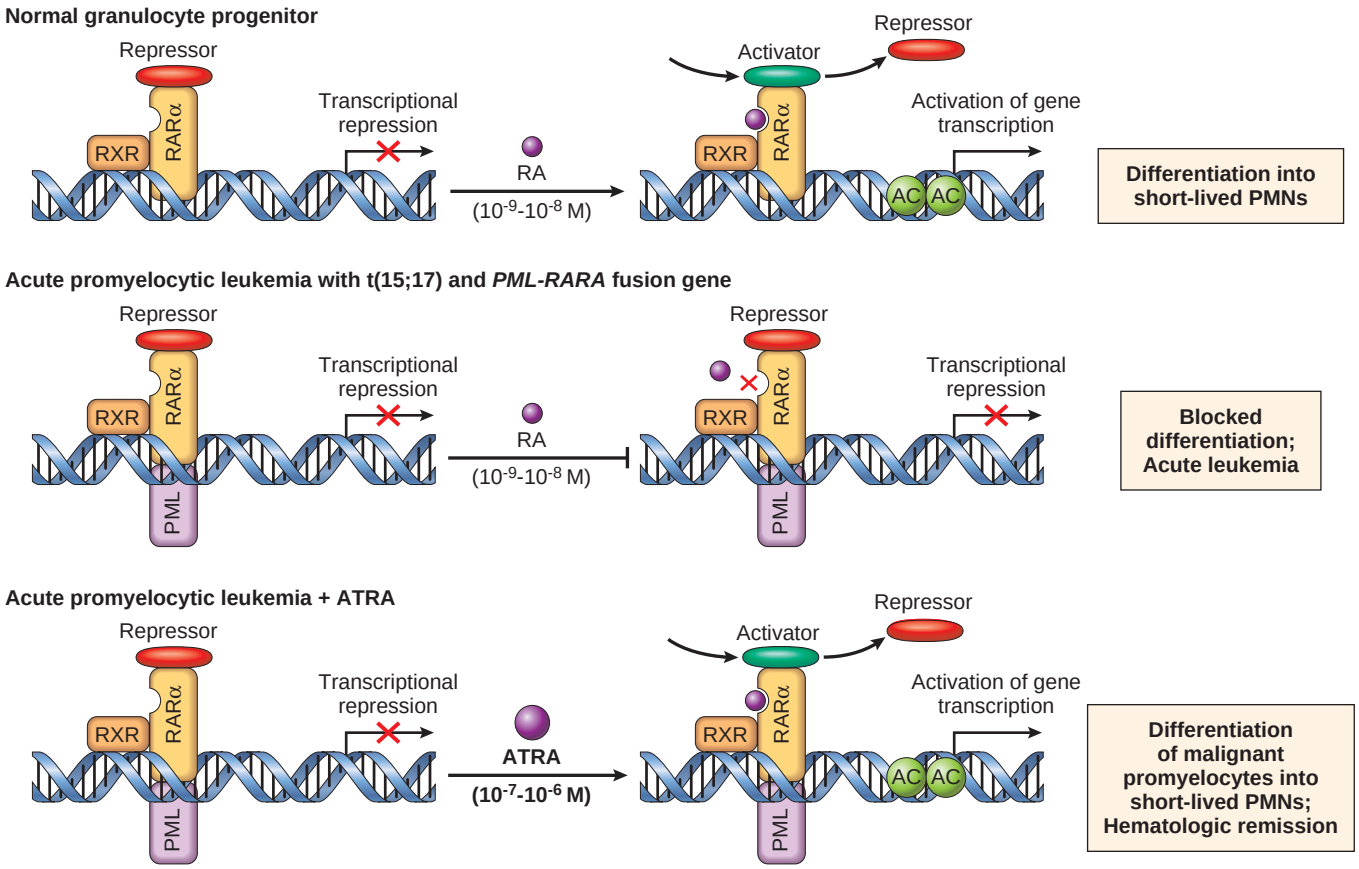

Figure 7-41 Molecular pathogenesis of acute promyelocytic leukemia and basis for response to all-trans retinoic acid. ATRA, all-trans retinoic acid; RA, retinoic acid; RXR, binding partner for normal RARa and PML-RARa fusion protein encoded by a chimeric gene created by the (15;17) translocation in acute promyelocytic leukemia.

involving tumor suppressor genes, as well as small insertions of DNA from one site into another. It should be noted that not all deletions lead to loss of gene function; a few activate oncogenes through the same mechanisms as chromosomal translocations. For example, about 25% of T-cell acute lymphoblastic leukemias have small deletions of chromosome 1 that juxtapose the *TAL1* proto-oncogene with a nearby active promoter, leading to overexpression of the TAL1 transcription factor. Similarly, deletions involving chromosome 5 in a subset of lung cancers produce an oncogenic *EML4-ALK* fusion gene encoding a constitutively active tyrosine kinase. It is likely that more "cryptic" deletions that activate oncogenes will be discovered through deep sequencing of cancer genomes.

Gene Amplification. Overexpression of oncogenes may also result from reduplication and amplification of their DNA sequences. Such amplification may produce up to several hundred copies of the oncogene in the tumor cell. In some cases the amplified genes produce chromosomal changes that can be identified microscopically. Two mutually exclusive patterns are seen: (1) multiple small extrachromosomal structures called *double minutes* and (2) *homogeneous staining regions*. The latter derive from the insertion of the amplified genes into new chromosomal locations, which may be distant from the normal location of the involved oncogene. The affected chromosomal regions lack a normal pattern of light and dark-staining bands, appearing homogeneous in karyotypes (Fig. 7-27). From a clinical perspective the most important amplifications are *NMYC* in neuroblastoma and *ERBB2* in breast cancers. *NMYC* is amplified in 25% to 30% of neuroblastomas, and its amplification is associated with poor prognosis. *ERBB2* amplification occurs in about 20% of breast cancers. As already mentioned, antibody therapy directed against the HER2 receptor encoded by *ERBB2* is an effective therapy for this molecular subset of breast cancers.

Chromothrypsis. The true extent of chromosome rearrangements in cancer is only now coming into view thanks to sequencing of entire cancer cell genomes, which allows for comprehensive "reconstruction" of chromosomes from DNA sequences. Genomic sequencing has revealed not only many simple rearrangements (e.g., small deletions, duplications, or inversions) that were not appreciated by prior methods, but also much more dramatic chromosome "catastrophes" termed *chromothrypsis* (literally, chromosome shattering). Chromothrypsis is observed in 1% to 2% of cancers as a whole, but is found in up to 25% of osteosarcomas and other bone cancers and at relatively high frequency in gliomas as well. It appears to result from a single event in which dozens to hundreds of chromosome breaks occur within part or across the entirety of a single chromosome or several chromosomes. The genesis of these breaks is unknown, but DNA repair mechanisms are activated in affected cells that stitch the pieces together in a