Much remains to be deciphered about the state of the "epigenome" in various cancers and its contribution to the malignant state, but several aspects of the relationship merit emphasis.

- The lineage-specificity of certain oncogenes and tumor suppressor genes has an epigenetic basis. You may have noticed that tumor suppressors and oncoproteins can be broadly divided into two classes, those that are mutated or otherwise dysregulated in many cancers (e.g., RAS, MYC, p53), and those that are mutated in a restricted subset of tumors (e.g., VHL in renal cell carcinomas, APC in colon carcinoma) and are thus lineage restricted. A cancer cell's lineage or differentiation state, like that of normal cells, is generated by epigenetic modifications that produce a pattern of gene expression that characterizes that particular cell type. It follows that lineage-restricted cancer genes only act within epigenetic contexts in which key oncogenic targets are controlled by these genes.
- The epigenome is an attractive therapeutic target. Because the epigenetic state of a cell depends on reversible modifications that are carried out by enzymes (which are generally good drug targets), there is intense interest in developing drugs that target epigenomic modifiers in cancer and other diseases. Inhibitors of histone deacetylases, chromatin erasers that remove acetyl groups from histones, are approved for use in certain lymphoid tumors, and DNA methylation inhibitors are now being used to treat myeloid tumors, based in part on the idea that these drugs may reactivate tumor suppressor genes. Other drugs that target specific chromatin writers and chromatin readers are also now being tested in clinical trials.
- Cancers may exhibit considerable epigenetic heterogeneity. Just as genomic instability gives rise to genetic heterogeneity in cancers, it is feared that cancers will also prove to have extensive epigenetic heterogeneity from cell to cell within individual tumors. One consequence of such heterogeneity may be drug resistance. For example, epigenetic alterations can lead to the resistance of lung cancer cells to inhibitors of EGF receptor signaling. When the inhibitors are removed, the lung cancer cells revert to their prior inhibitor-sensitive state. If widespread, such epigenetic plasticity may join genetic heterogeneity as yet another barrier to the development of curative cancer therapies.

Noncoding RNAs and Cancer

As discussed in Chapter 1, microRNAs (miRs) are small noncoding, single-stranded RNAs, approximately 22 nucleotides in length, that mediate sequence-specific inhibition of messenger RNA (mRNA) translation through the action of the RNA-induced silencing complex (RISC). Given that miRs control normal cell growth, differentiation, and cell survival, it is not surprising that they play a role in carcinogenesis. Altered miR expression, sometimes stemming from amplifications and deletions of miR loci, has been identified in many cancers. Decreased expression of certain miRs increases the translation of oncogenic mRNAs; such mIRs have tumor suppressive activity. Conversely, overexpression of other mIRs represss the expression of tumor suppressor genes; such mIRs promote tumor development and are often referred to as *onco-mIRs.* Specific examples of contributions of mIRs to cancer are numerous; the following are among the best established:

- **OncomiRs**. miR-200 has been shown to promote epithelial-mesenchymal transitions believed to be important in invasiveness and metastasis; and miR-155, originally identified at the site of retroviral insertions in avian lymphomas, is overexpressed in many human B cell lymphomas and indirectly upregulates a large number of genes that promote proliferation, including *MYC*.
- **Tumor suppressive miRs**. Deletions affecting certain tumor suppressive miRs, such as miR-15 and miR-16, are among the most frequent genetic lesions in chronic lymphocytic leukemia, a common tumor of older adults. In this context, it appears that their loss leads to upregulation of the anti-apoptotic protein BCL-2.
- **Tumor suppressive properties of mIR processing factors**. Study of families that are prone to the development of an unusual collection of neoplasms, including certain rare ovarian and testicular tumors, unexpectedly identified heterozygous germline defects in *DICER*, a gene that encodes an endonuclease that is required for the processing and production of functional mIRs. Thus, *DICER* is tumor suppressive in certain cellular contexts. Whether the tumor suppressive function of DICER stems from its involvement in processing of miRs remains to be established.

The involvement of miRs is likely the proverbial tip-of-the-iceberg with respect to the role of noncoding RNAs in cancer. Systematic genomic analyses have revealed that more than 60% of the genome is transcribed into RNAs, most of which are noncoding and believed to have regulatory functions (Chapter 1). These noncoding RNAs fall into several classes: piwi-interacting RNAs (piRNAs), the most common type of small noncoding RNA, which (like miRs) are believed to have a role in post-transcriptional gene silencing; snoRNAs, which are important in maturation of rRNA and the assembly of ribosomes; and long intervening noncoding RNAs (lincRNAs), some of which regulate the activity of chromatin "writers," the factors that modify histones and thereby control gene expression. Abnormalities in the expression of these regulatory RNAs have also been implicated in several human diseases, including cancer, and many more examples of cancer-associations are likely to be forthcoming.

Molecular Basis of Multistep Carcinogenesis

Given that malignant tumors must acquire multiple "hallmarks" of cancer, it follows that cancers result from the stepwise accumulation of multiple mutations that act in complementary ways to produce a fully malignant tumor. The notion that malignant tumors arise from a protracted sequence of events is supported by epidemiologic, experimental, and molecular studies, and the study of oncogenes and tumor suppressor genes has provided a firm molecular footing for the concept of multistep carcinogenesis. Genome-wide sequencing of cancers has revealed as few as ten or so mutations in certain leukemias