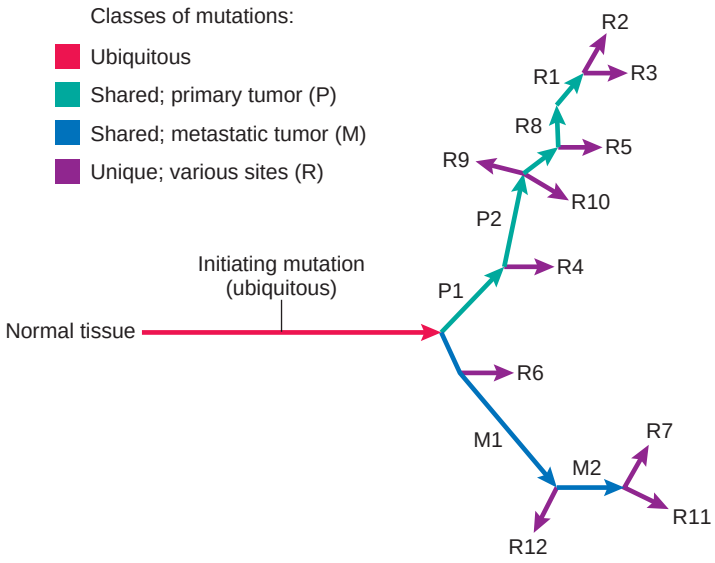

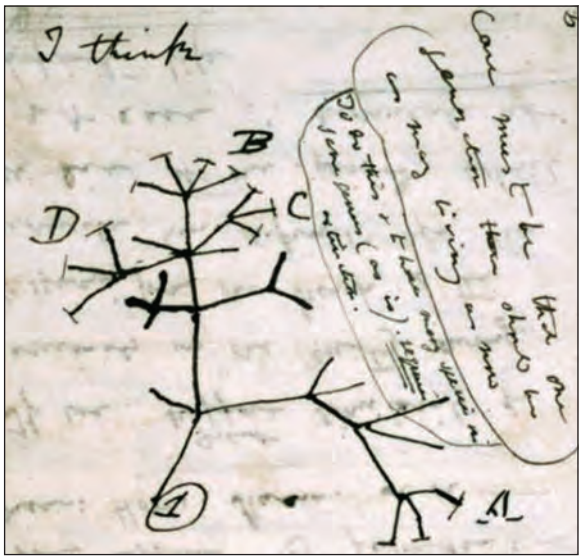

Figure 7-23 Tumor evolution. Evolution of a renal cell carcinoma *(left panel)* and Darwin's finches *(right panel).* The renal cell carcinoma evolutionary tree is based on genetic comparisons drawn from sequencing of DNA obtained from different tumor sites; the finch evolutionary tree was surmised by Darwin based on morphologic comparisons of different species of finches on the Galapagos Islands. (*right panel*, from Notebook B: Transmutation of Species, Charles Darwin, 1837, p.26.)

selective pressures that cancer cells face is effective chemotherapy or radiotherapy given by treating physicians. Tumors that recur after therapy are almost always found to be resistant if the same treatment is given again, presumably because therapy selects for preexistent subclones that, by chance, have a genotype that allows them to survive.

It is increasingly apparent that **in addition to DNA mutations, epigenetic aberrations also contribute to the malignant properties of cancer cells.** Epigenetic modifications include DNA methylation, which tends to silence gene expression, and modifications of histones, the proteins that package DNA into chromatin, which depending on their nature may either enhance or dampen gene expression. Together, *DNA methylation* and *histone modifications* dictate which genes are expressed, which in turn determines the lineage commitment and differentiation state of both normal and neoplastic cells. Epigenetic modifications are usually passed on faithfully to daughter cells, but on occasion (just as with DNA mutations) alterations may occur that result in changes in gene expression. Aberrant DNA methylation in cancer cells is responsible for the silencing of some tumor suppressor genes, while tumor-specific changes in histone modifications may have far-ranging effects on gene expression in cancer cells (see later). The increasing awareness of the role of epigenetic alterations in cancer has revealed a new path forward for cancer treatment; unlike DNA mutations, epigenetic changes are potentially reversible by drugs that inhibit DNA- or histone-modifying factors. Thus, there is considerable interest in treating cancers with drugs that correct epigenetic abnormalities in cancer cells, with some encouraging early results.

We will return to these themes throughout the subsequent discussions, which turns to the cellular and molecular properties that underlie the malignant behavior of cancer cells.

Cellular and Molecular Hallmarks of Cancer

Over the past several decades, hundreds of genes that are mutated in cancer have been discovered. It is traditional to describe the functional consequences of these alterations one gene at a time. However, the blizzard of mutated genes emerging from the sequencing of cancer genomes has blanketed the landscape and revealed the limitations of trying to grasp the fundamental properties of cancer, gene by gene. For example, it is estimated that compilation of a reasonably complete catalog of the major genetic alterations in breast carcinoma will require whole genomic sequencing of thousands of tumors and will lead to the identification of dozens to hundreds of distinct driver mutations—and this is just one of hundreds of different kinds of cancer, some of which are substantially more genetically complex than breast carcinoma.

A much more tractable and conceptually satisfying way to think about the biology of cancer is to consider the common phenotypic properties that are imparted to cancer cells by their diverse genomic and epigenomic alterations. It appears that **all cancers display eight fundamental changes in cell physiology, which are considered the hallmarks of cancer**. These changes are illustrated in Figure 7-24 and consist of the following:

- **Self-sufficiency in growth signals**. Tumors have the capacity to proliferate without external stimuli, usually as a consequence of oncogene activation.
- **Insensitivity to growth-inhibitory signals**. Tumors may not respond to molecules that inhibit the proliferation of normal cells, usually because of inactivation of tumor suppressor genes that encode components of these growth inhibitory pathways.
- **Altered cellular metabolism**. Tumor cells undergo a metabolic switch to aerobic glycolysis (called the

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