Part I
Basic Aspects

Understanding Carcinogenesis. Hippokratis Kiaris

ISBN 3-527-31486-5

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Some Introductory Concepts in Tumor Biology: Clonal Evolution and Autonomy versus Non-autonomy of Cancer Cells

Cancer has a Genetic Basis

Cancer is a genetic disease. This statement is a consensus that can be found in many cancer books and science articles, and reflects the fact that changes at the level of the genetic material, the DNA, are responsible for disease development. In addition to the hereditary types of the disease in which this genetic basis is apparent and self-evident, all types of sporadic cancer progress through alterations at the level of the cell's genome. Tumor-causing viruses, mutagens and all other factors associated with carcinogenesis either directly or indirectly affect the DNA at a certain time.

Clonality

Cancer is also clonal. Indeed, cancer is initiated by a single cell that carries (inherits or is being targeted by) a mutation. Subsequently, this cell expands clonally. However, this expansion is continually subjected to selection as the cancer cells constantly accumulate mutations that change their behavior. The mutations that contribute the more aggressive characteristics, like rapid growth and resistance to certain therapeutic modalities, are those that predominate. Therefore, a tumor becomes clinically worse with time. By examining the genotype of the cancer cells in a given tumor it is possible to identify such mutations, and to trace their physical history based on the subset and the histopathology of the cells that carry a specific genetic lesion. This "dynamic" nature of cancer cells is responsible for the failure of conventional therapies and our inability to develop appropriate diagnostic tools that can be applied to even a single distinct type of cancer.

Autonomy of Cancer Cells

Cancer cells are also characterized by increased autonomy compared to normal cells of the same origin. Changes in the environment of the cancer cells generally make them more tolerant than their normal counterparts. This property of malig-

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nant cells is reflected in the fact that under culture conditions it is much easier to grow cancer cells than normal cells, while culturing the latter always bears the danger of selecting for the cells that become transformed. However, despite this apparent property of cancer cells, continuous cancer growth exhibits a high dependency on the microenvironment to a degree that current opinion views malignant (and not only) tumors as an heterologous entity of different (genetically and histologically) cell types that interact reciprocally with each other.

Heterogeneity of Cancers

Finally, cancer is not one, but many diseases. Indeed, countless combinations of genetic lesions contribute to the development of virtually unlimited clinical entities that, while they are all referred to as malignant tumors, exhibit dramatic differences in their histopathological and clinical characteristics. Even tumors of exactly the same histopathology and classification may exhibit quite important differences in their clinical outcome.

Although these statements are in principle accurate, they carry certain limitations with important consequences in tumor biology, as will become apparent in the following chapters. We will try to view carcinogenesis in a simplistic manner that, however, permits the perception of its complexity and, were possible, its unity.