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Molecular Origins of Cancer

Harold J. Burstein, M.D., Ph.D., and Robert S. Schwartz, M.D.

Over the past decade, insights into the origins and behavior of human cancers have reshaped our understanding of these diseases and have generated advances in clinical care. The seminal feature of this research is the focus on human cancers. By using ideas and technologies originally derived from basic science laboratories, investigators have shifted the forefront of cancer research from *in vitro* models of tumor growth to the characterization and treatment of cancers in humans.

This issue of the *Journal* launches a series of reviews on the molecular origins of cancer. The goal of this series is to highlight advances in the biology of cancer and their relevance to clinical practice. The topics relate to three broad areas of tumor biology.

The first area concerns genetic changes in the cancer cell — inborn and acquired — that give rise to the transformed phenotype. Chromosomal abnormalities and alterations in oncogene expression are widely documented in all cancers and often serve as the calling card for unique tumor subtypes and as targets for new kinds of treatment. Other acquired epigenetic changes that alter the structure and expression of genes contribute to tumor progression and may also serve as treatment targets. Molecular methods have defined many hereditary cancer syndromes, each driving unique abnormalities in cell function, and each with distinct clinical features. The development of genetic testing has allowed patients and family members to make better-informed assessments of personal cancer risk and to weigh prophylactic and surveillance options.

The second area centers on the interactions between the tumor and the patient — the modern expression of the “seed and soil” hypothesis. In contrast with most laboratory tumor models, cancers in humans arise and spread through multi-

ple and specific physiological niches. Cancers interact with surrounding tissue stroma and micro-environments both at the original cancer site and at sites of metastasis, and they are disseminated through lymphatic and vascular channels. “Host” responses include changes in vascularity and immune responses to tumors. Advances in the fields of tumor angiogenesis and tumor immunology are leading to novel treatments for many cancers, alongside therapies that seek to alter the biology of metastasis and of the microenvironment.

The third category concerns the tools that can characterize common tumors in humans, such as breast, lung, colorectal, and prostate cancers, at the level of the gene. Genomic analysis increasingly serves as a valuable complement to traditional pathology, capturing a degree of tumor-to-tumor variation that can refine the classification of tumors into clinically relevant subsets, thereby also refining prognosis and treatment selection.

Two lessons emerge from studies of the molecular origins of cancer: the remarkable biologic heterogeneity of cancers in humans and the intimate relationship between that variation and clinical results in oncology. Much of the heterogeneity in treatment outcomes for patients with cancer stems directly from the underlying variation in tumor biology, which dictates the likelihood and pace of tumor dissemination and the tumor’s sensitivity to both traditional and novel cancer treatments. The corollary is that the better our appreciation for the unique biologic features of each tumor, the better will be our ability to tailor treatment to each patient, bringing the right type and the right amount of therapy to bear on the cancer.

From the Dana–Farber Cancer Institute, Brigham and Women’s Hospital, and Harvard Medical School (H.J.B.).

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