CANCER METASTASIS

Metastasis is responsible for a large burden of morbidity and mortality among cancer patients; currently, however, few therapies specifically target metastatic disease. Further scientific dissection of the underlying pathways is required to pave the way for new therapeutic targets. This groundbreaking new text comprehensively covers the processes underlying cancer metastasis and the clinical treatment of metastatic disease. Whereas previous volumes have been compendia of laboratory research articles, the internationally renowned authors of this volume have summarized the state-of-the-art research in the metastasis field. A major section covers the cellular and molecular pathways of metastasis and experimental techniques and the systems and models applied in this field. Subsequently, the clinical aspects of the major cancer types are considered, focusing on disease-specific research and therapeutic approaches to metastatic disease. The focus is on novel pathophysiological insights and emerging therapies; future directions for research and unmet clinical needs are also discussed.

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CANCER METASTASIS

BIOLOGIC BASIS AND

THERAPEUTICS

Edited by

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This book is dedicated to all advanced cancer patients and their families with the hope of inspiring a brighter future with improved treatment of metastatic disease.

– David Lyden, Danny R. Welch, and Bethan Psaila
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After a diagnosis of primary cancer is established, the urgent question is whether the cancer is localized or if it has already spread to the regional lymph nodes and distant organs. Despite improvements in surgical techniques, general patient care, and local and systemic adjuvant therapies, most deaths from cancer still result from the progressive growth of metastases that are resistant to conventional therapies.

The process of tumor metastasis is highly selective and consists of a series of sequential, interrelated steps, all of which must be completed by metastatic cells to produce clinically relevant lesions. After the initial transformation and growth of cells, vascularization must occur if a tumor mass is to exceed 1 mm in diameter. Next, local invasion of the host stroma occurs as a consequence of the enhanced expression of a series of enzymes such as collagenase. After the invading cells penetrate the lymphatic or vascular channels, they may grow there, or a single cell or clumps of cells may detach and be transported within the circulatory system. The tumor emboli must survive immune and nonimmune defenses and the turbulence of the circulation, then lodge in the capillary bed of receptive organs, extravasate into the organ parenchyma, proliferate, and establish a micrometastasis. Finally, the growth of these microscopic lesions requires development of a vascular supply and evasion of host defense cells.

The search for factors that regulate metastasis began in 1889 when Paget analyzed postmortem data of women who died of cancer and noticed the high frequency of metastasis to the ovaries and the different incidence of skeletal metastases associated with different primary tumors. Paget concluded that the organ distribution of metastases is not a matter of chance and suggested that metastases develop only when certain tumor cells are compatible with specific organs. These findings contradicted the prevailing theory proposed by Virchow that metastasis can be explained merely by the lodgment of tumor cell emboli in the vasculature. Paget concluded that “remote organs cannot be altogether passive or indifferent regarding embolism” and provided the everlasting “seed-and-soil” principle. In 1929, James Ewing challenged Paget’s theory and proposed that metastatic dissemination occurs by purely mechanical factors that are determined by the anatomical structure of the vascular system. Ewing’s viewpoint prevailed for decades.

In the 1970s, the selective nature of metastasis was demonstrated by Fidler and the biologic heterogeneity of neoplasms was reported by Fidler and Kripke. In the 1980s, Hart and Fidler provided the definitive proof of Paget’s hypothesis by demonstrating that although tumor cells reached the vasculature of all organs, metastases developed only in compatible organs. Collectively, these studies established three key principles. First, neoplasms are biologically heterogeneous. Second, the process of metastasis is highly selective, favoring the survival and growth of a small subpopulation of cells that preexist in the heterogeneous parent neoplasm. Third, the outcome of metastatic growth depends on multiple interactions of metastatic cells with host homeostatic mechanisms that the tumor cells can usurp.

The following chapters provide the reader with an intelligent and detailed analysis of the various steps in the pathogenesis of metastasis. It is most encouraging to discover that the process can now be studied on the systemic, cellular, and molecular levels. Understanding the mechanisms that regulate metastasis must continue to be a primary goal of cancer research. Only from a better understanding can we design better approaches to therapy of this fatal phase of cancer. Succinctly stated: Biology is the foundation of therapy.

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