Preface

Danny R. Welch

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Although long recognized as the most lethal attribute of neoplasia, metastasis still remains a relatively poorly understood and difficult-to-treat entity. This issue of *Cancer and Metastasis Reviews* began as an invitation from the editors for reviews on metastasis regulatory genes. However, no review on metastasis genes would be complete in the absence of the context—understanding that metastasis-regulatory genes are regulated by signals from the microenvironment and that cancer phenotypes are plastic. Likewise, newer knowledge of metastasis-regulatory genes is being introduced into clinical practice.

Long thought to be the terminal step in a stochastic progression of tumor populations, metastasis is currently undergoing a re-evaluation of the underlying molecular biology and biochemistry in addition to the nuances of the biology taking place in a tumor. It is becoming increasingly well recognized that dissemination of cells can occur early in neoplastic progression. However, the formation of bona fide metastatic disease is much less common. The underlying questions being asked in this volume are: What are the underlying intrinsic characteristics that allow tumor cells to disseminate and eventually form overtly metastatic disease? What are the cell–cell and cell–matrix interactions that occur to manipulate metastatic tumor cell gene expression? What can be done utilizing information regarding the genetics and gene expression of cancer cells in clinical cancer treatment and control?

Certain principles emerge from data presented herein and elsewhere in the metastasis research literature. Namely, there are prometastatic and antimetastatic influences impinging upon tumor cells. There are growing number of metastasis-suppressing genes that have been cloned and characterized at a functional level; yet, their mechanisms of action are still largely unknown. Likewise, there are a number of genes whose coordinate expression must occur in order for tumor cells to initially disseminate and eventually colonize ectopic sites. Unfortunately, myriad genes are involved in metastasis. That fact alone precludes a comprehensive compendium. Rather, Yibin Kang and I decided to focus on representative pro- and antimetastatic genes (and pathways). Description of these molecules provides principles from which one can extrapolate to others.

To recognize the importance of cancer cell epigenetic processes within microenvironments in which tumor cells find themselves, we asked the authors to incorporate discussion of relevant tumor–stromal and tumor–matrix and tumor–host cell interactions into their respective papers. Among the environments to which tumor cells respond are the so-called premetastatic niches. Growing evidence indicates that tumor cells orchestrate mobilization of stem cells that renovate sites into which disseminated tumor cells eventually divide and thrive. The state-of-the-art is that researchers are actively working to identify the outgoing signals from metastatic cells. Clearly, tumor cell responses to incoming microenvironmental signals involve changing gene expression and, sometimes, reversion to embryonic processes such as those involved in epithelial–mesenchymal transition. A strong theme from all of the contributions to this volume is that there are multiple ways by which a cell can complete the metastatic process. A one-size-fits-all

D. R. Welch (✉)
The Kansas University Medical Center,
3901 Rainbow Blvd. Robinson 4030 Mailstop 1027,
Kansas City, KS 66160, USA
e-mail: DWELCH@kumc.edu

explanation simply does not exist. Likewise, a growing literature reveals that many of the metastasis-associated gene products are involved in post-translational modifications (e.g., proteolytic cleavage, glycosylation, phosphorylation) or are involved in regulating protein translation itself (e.g., regulatory RNA).

This volume concludes with a recognition that tumor cells disseminate early and throughout neoplastic progression. By coupling genetic, transcriptomic, and proteomic information with monitoring circulating or disseminated tumor cells, it appears that physicians can obtain useful prognostic and predictive information to guide therapy.

Thus, this volume of Cancer and Metastasis Reviews is intended to be an up-to-date reference on the wide variety of metastasis-regulatory genes and the plasticity of their expression. It is hoped that the information provided in this volume will encourage additional studies that will lead to improved approaches to the prevention and treatment of cancer metastasis.

This volume is dedicated to the brave men and women fighting metastatic disease. Thank you for your ever-present dignity and for providing inspiration to scientists and clinicians studying metastasis around the world.