Cell Motility in Cancer Invasion and Metastasis

Cancer Metastasis – Biology and Treatment

VOLUME 8

Cell Motility in Cancer Invasion and Metastasis

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Springer

A C.I.P. Catalogue record for this book is available from the Library of Congress.

ISBN-10 1-4020-4008-3 (HB)
ISBN-13 978-1-4020-4008-5 (HB)
ISBN-10 1-4020-4009-1 (e-book)
ISBN-13 978-1-4020-4009-2 (e-book)

Published by Springer,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

www.springer.com

Printed on acid-free paper

Printed in the Netherlands.

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PREFACE

This book, "Cell Motility in Cancer Invasion and Metastasis", is the fifth contribution in the Series "Cancer Metastasis – Biology and Treatment". Here, we focus neither on a molecule or set of molecules nor on a tissue, but on a cell behavior – motility. As the research community as a whole investigates organismal biology at more and more complex levels, the dynamic nature of the underlying processes come to the fore. Cell movement and migration is an integration of such dynamic multifaceted processes, involving not only the moving cell itself and its supporting matrix, but also adjacent and distant cells. While cell motility has been appreciated and studied for decades, only more recently has its critical role in the pathophysiology of tumor dissemination been probed extensively. This book was commissioned to note the current state of understanding in this arena, and highlight new avenues and key questions for future investigation.

The chapters that comprise this book are presented in three themes. Prior to these themes, I present an introductory chapter that overviews cell motility and presents evidence that suggests that tumor invasiveness may be considered a disease of dysregulated motility. This chapter provides a common framework for the ensuing contributions. The first theme of three chapters focuses on technological breakthroughs that will enable novel modes of study. Yuan and colleagues describe matrices available for study and newer ones being developed. As motility is a biophysical process that depends on the substratum not only for dynamic tractive and contractile forces but also for active signals, the choice of model system determines the range of responses noted. It has been realized that complex matrices are required to provide in vitro models relevance to the human condition. The next chapter mainly describes innovative work from the laboratories of Segall and Condeelis utilizing a novel intravital imaging capability. These

studies take the investigation of migration during tumor progression directly into the tumor itself in a living animal. This retains the relevant host environment. Yates, Stolz and Griffith describe novel intermediary modes of study in which organ environments are recreated *ex vivo* to enable higher throughput and more direct manipulations in a system that retains much of the in vivo complexity.

Five chapters comprise the second theme of molecular regulators of tumor cell motility. These select five key classes of molecules that are amenable for intervention. While not comprehensive, the chapters focus on arguably the molecular classes best examined and justified in the context of tumor progression. Starting from outside the cell, Joslin and Lauffenburger explore the concept that peptide growth factors often drive motility in an autocrine modality as a form of cellular sonar; this is in addition to the well-described paracrine chemotactic signaling. As a wide variety of tumors, and practically all carcinomas present autocrine signaling loops involving the motogenic erbB family of receptors, these are highlighted. The next chapter by Comoglio and Boccaccio focuses on peptide growth factors that are defined by their exquisite ability to loosen the bonds between cells and enable an transition to the mesenchymal state. This sets the stage for invasive growth as individual cells break from the primary tumor mass and attain the ability to survival and proliferate as individual cells. At the interface of the cell and surrounding barrier stroma are the proteinases that remodel both the matrix and the cell surface allowing for new cellular interpretations of the external milieu; new advances in these studies are described by Stetler-Stevenson and Seo. Rabinovitz and Mercurio detail the molecules that most ubiquitously provide both traction and interpretation of that supporting matrix, the integrins. In particular, one integrin appears to redirect its activities from maintaining sessile hemidesmosomes in normal epithelia to driving invasiveness in a variety of carcinomas. In the last chapter in this theme, Collard and colleagues describe regulators of the actual motive force, the actin cytoskeleton. In response to signals from growth factor and traction receptors, among others, a family of small GTPases control cytoskeleton assembly, disassembly and connectivity to the substratum.

The last theme aims to integrate these molecules and processes in tumors that exemplify the issues of motility in tumor dissemination. Four neoplasias were selected based on clear human correlative and experimental causative implications of increased motility leading to both localized invasiveness and distant metastases. In all these cases, even the local invasiveness results in significant morbidity and mortality. The first tumor discussed by Stettner, Natarajan and Gladson is highly invasive, with motility being strongly linked to growth factor signaling, adhesiveness, and cell-matrix interactions. A

second tumor with significant local invasiveness driven by autocrine growth factor signaling is squamous carcinoma of the oral cavity, as related by Thomas and Grandis. Bosserhoff presents a tumor, melanoma, in which invasiveness is a first step to distant metastases. Lastly, prostate cancer represents a complex invasion/metastasis situation in which motility plays a central, and rate-limiting role.

The compilation of these chapters is a compendium that relates current concepts and techniques, and highlights key questions in the role of motility in tumor dissemination. We hope that these chapters stimulate further research in this emerging field. As editor of this book, I must apologize to the readers and investigators looking for chapters addressing other aspects of tumor dissemination or other tumor types. Particular to the subject matter, this book focuses on the invasion and metastasis of solid tumor, as motility of hematopoietic cells and their neoplasias present unique issues and challenges. In addition, only select key regulators are described at length, not because others are not involved, but due to the strong linkage of these to both motility and tumor dissemination. No doubt future studies will uncover additional key effectors that can be targeted. It is only by focusing on these select topics and representative tumors that we can provide a cohesive and internally comprehensive view that may serve as a starting point for future investigations.

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1 April 2005