Cell Motility Factors

Edited by I. D. Goldberg

E. M. Rosen, Associate Editor

Birkhäuser Verlag
Basel · Boston · Berlin

Editors' addresses:

I. D. Goldberg, M.D.
Department of Radiation Oncology
Long Island Jewish Medical Center
270-05 76th Avenue
New Hyde Park, NY 11042
USA

CIP-Titelaufnahme der Deutschen Bibliothek Deutsche Bibliothek Cataloging-in-Publication Data

Cell motility factors/ed. by I. D. Goldberg.—Basel; Boston; Berlin: Birkhäuser, 1991
(Experientia: Supplementum; 59)
ISBN 978-3-0348-7496-0 ISBN 978-3-0348-7494-6 (eBook)
DOI 10.1007/978-3-0348-7494-6
NE: Goldberg, Itzhak D. [Hrsg.]; Experientia/Supplementum

Library of Congress Cataloging-in-Publication Data

Cell motility factors/edited by I. D. Goldberg.
p. cm.—(EXS, Experientia supplementum; 59)
Based on the International Conference on Cytokines and Cell Motility, held in May 1990 in New York, sponsored by Long Island Jewish Medical Center and the National Cancer Institute, Laboratory of Pathology.
Includes bibliographical references and index.
ISBN 978-3-0348-7496-0
1. Cells—Motility—Congresses. 2. Cancer cells—Motility—Congresses. 3. Chemotaxis—Congresses. I. Goldberg, I. D. (Itzhak David), 1948- . II. Long Island Jewish Medical Center. III. National Cancer Institute (U.S.) Laboratory of Pathology. IV. International Conference on Cytokines and Cell Motility (1990: New York, N.Y.) V. Series: Experientia. Supplementum; v. 59.
[DNLM: 1. Cell Movement—congresses. 2. Cell Transformation, Neoplastic—congresses. 3. Cytokines—physiology—congresses. 4. Neoplasm Invasiveness—congresses. 5. Neoplasm Metastasis—congresses. W1 EX23 v. 59/QH 647 C39303 1990]
QH647. C448 1991
574.87'64—dc20

Softcover reprint of the hardcover 1st edition 1991

P.O. Box 133
4010 Basel
Switzerland

ISBN 978-3-0348-7496-0

Dedicated to my parents
Aryeh and Pnina Goldberg

and my wife and children
Rina, Elisha, Irit, Shlomit and Avital

Contents

Preface

Cell motility is an important component of many basic physiologic and pathologic processes. Understanding mechanisms of cell motility is therefore essential to the development of new research and clinical approaches in biomedical research.

In the early phases of embryogenesis, prepreogrammed morphogenetic movement determines normal development. The migration of the neural crest cells, for example, is responsible for the establishment of almost the entire peripheral nervous system, the proper positioning of the epinephrine-secreting cells in the adrenal gland and the deposition of pigment cells in the skin (Newgreen and Erikson, 1986). Any disturbance or deviation from this complex migration pattern results in serious malformations. The embryonic cells are stimulated to migrate by internal signals as well as by signals from adjacent cells. Various stimulatory and inhibitory mechanisms are likely to operate during this dynamic process. However, once morphogenesis is achieved, most somatic cells tend to remain stationary, and the motile phenotype is dormant.

Under certain physiologic and pathologic conditions, however, cells re-express their motile phenotype and migrate. In wound healing and angiogenesis cell migration and proper three-dimensional positioning is critical. Endothelial cell migration following luminal injury is another homeostatic mechanism which helps prevent vascular lesions (Reidy and Silver, 1985; Sholley et al., 1977; Wong and Gottlieb, 1988). In pathological conditions such as atherosclerosis, smooth muscle cell migration through the internal elastic lamina to the luminal surface may be the initial event leading to the development of the atherosclerotic plaque (Goldberg, 1982).

Recamier, who introduced the term metastasis in 1829, also described invasion of tumor cells into veins. In 1916, Lambert, in the Journal of Cancer Research, introduced the concept of active cell motility in the process of invasion and metastases suggesting that "... it is not necessary to regard the formation of metastatic tumor nodules as always the result of the passive transportation of cells from a primary tumor by the blood or lymph stream when cells may easily get from place to place by their own powers of locomotion."

The ability of tumor cells to move out of the primary site and invade adjacent tissues directly impacts upon cure rate. Almost all patients with

localized intraductal carcinoma of the breast, where tumor cells grow within the duct and do not invade adjacent tissues, are cured of their disease. On the other hand, patients whose tumors contain diffusely infiltrating cells which migrate into the surrounding vascular and lymphatic channels have a significantly poorer prognosis, and many succumb to metastatic disease (Harris et al., 1987).

What are the factors that play a role in cell motility? The cytoskeletal system, the basic structure that maintains the shape of the cell and provides for locomotor functions, is central to cell movement (Rosen and Goldberg, 1989). The substrate, the environment on which the cell is maintained, can prevent or induce cell motility (Ruoslahti and Pierschbacher, 1987; Hynes, 1987; Yamada, 1983). Cell-cell interactions via cell surface molecules and structures are modified as cells move (Peyrieras et al., 1983; Behrens et al., 1985; Bhargava et al., 1991). Proteases, which break down connective tissue, are secreted by motile cells and clear a path through which cells can move (Folkman, 1985; Liotta et al., 1982). In addition, some of the growth and differentiation factors have also been shown to affect cell motility (Barrandon et al., 1987; Blay and Brown, 1985; Grotendorst et al., 1981).

While our knowledge of the basic mechanisms of cell motility has been increasing significantly, it is only very recently that a new group of specific regulators of cell motility has been described. These cytokines, which include autocrine motility factor (AMF), migration stimulating factor (MSF) and scatter factor (SF), are major topics of this monograph. Preliminary data suggest that motility factors may play significant roles in processes such as wound healing, angiogenesis, embryogenesis and tumor invasion.

The expression of a motile phenotype induced by motility factors may be the result of autocrine production of motility factors. Autocrine stimulation of cell motility may parallel autocrine growth stimulation of tumor cells (e.g., by autocrine production of PDGF). Such mechanism can explain the autonomous production of autocrine motility factor (AMF) by bladder carcinoma cells (Liotta et al., 1986). Interestingly, Liotta et al., have shown that while AMF is produced only by transformed NIH 3T3 fibroblasts, both nontransformed and transformed fibroblasts respond to it suggesting that normal cells express receptors.

Alternatively, the signal for motility may be produced by surrounding normal cells rather than the tumor cells themselves. Tumor cells may induce surrounding normal cells to produce factors which facilitate tumor invasion. Such an induction mechanism has been recently reported by Basset et al. (1990), who described stromolysin-3, a novel metalloproteinase gene, which is produced by stromal cells of breast carcinoma and is thought to facilitate tumor cell invasion (Sholley et al., 1977). In an earlier study Chelberg et al. (1990) showed that fragments of extracellular matrix may be chemotactic to tumor cells

supporting the hypothesis of complex interactions between tumor and surrounding cells during invasion. Such mechanisms may explain potential induction of scatter factor production of fibroblasts which, in turn, results in paracrine stimulation of epithelial cell-derived tumors.

The production of migration-stimulating factor (MSF) by fibroblasts of patients with breast cancer and some members of their families without clinically evident malignancy (Schor et al., 1991), may provide a marker which reflects an abnormal interaction between epithelium and mesenchyme related to the development of malignancy.

The study of motility factors is in its infancy. As we gain deeper insight into the complex roles of these molecules, we may be able to devise new therapeutic approaches to enhance or control cell motility in health and disease. This monograph does not attempt to provide a comprehensive review of this rapidly evolving field. In May of 1990, Long Island Jewish Medical Center in New York and the National Cancer Institute, Laboratory of Pathology, cosponsored an International Conference on Cytokines and Cell Motility. Many of the chapters in this monograph are extensions and updated information of the lectures presented at the conference. The book provides the reader with basic concepts of cell motility as related to amoeboid and neutrophil chemotaxis, basic adhesion mechanisms in embryogenesis and metastasis, extensive review of cytokines and cell motility factors and, finally, the role of computer automation in image analysis of cell motility. It is hoped that this volume will stimulate further interest and research in this area.

I would like to thank Dr. Elliott Schiffmann for helping to organize the cell motility conference and the participating authors for their excellent contributions. I would like to thank the Long Island Jewish Medical Center and its President, Robert K. Match, M.D., for their outstanding support of research in the Department of Radiation Oncology and the Joel Finkelstein Cancer Foundation for providing a generous grant. Finally, I would like to thank the Associate Editor, Dr. Eliot Rosen, with whom we have been collaborating the last ten years and Dr. Madhu Bhargava, Director of Research in the Department of Radiation Oncology at Long Island Jewish Medical Center, for their contributions to our research efforts and to Diane Thompson for her assistance in the coordination of this publication.

References

Barrandon, Y., and Green, H. (1987) Cell migration is essential for sustained growth of keratinocyte colonies: The role of transforming growth factors and epidermal growth factor. Cell 50: 1131–1137.

Basset, P., Bellocq, J. P., Wolf, C., Stoll, I., Hutin, P., Limacher, J. M., Podhajcer, O. L., Chenard, M. P., Rio, M. C., and Chambon, P. (1990) A novel metalloproteinase gene specifically expressed in stromal cells of breast carcinomas. Nature 348: 699–704.

Behrens, J., Birchmeier, W., Goodman, S. L., et al. (1985) Dissociation of Madin-Darby kidney epithelial cells by the monoclonal antibody anti-Arc-1: Mechanistic aspects and identification of the antigen as a component related to uvomorulin. J. Cell Biol. 101: 1307–1315; 1985.

Bhargava, M. M., LI, Y., Joseph, A., Pendergast, M., Hofmann, R., Rosen, E. M., and Goldberg, I. D. (1991) Purification, characterization and mechanism of action of scatter factor from human placenta, in: Goldberg, I. D. (ed) Cell Motility Factors. Birkhauser Verlag, Switzerland, pp. 63–75. (this volume)

Blay, J., and Brown, K. D. (1985) Epidermal growth factor promotes the chemotactic migration of cultured rat intestinal epithelial cells. J. Cell Physiol. 124: 107–112.

Chelberg, M. K., McCarthy, J. B., Skubitz, A. P. M., Furcht, L. T., and Tsilibary, E. C. (1990) Characterization of a synthetic peptide from type IV colagen that promotes melanoma cell adhesion, spreading, and motility. J. Cell Biol. 111: 262–270.

Folkman, J. (1985) Tumor angiogenesis. Adv. Cancer Res. 43: 175–203.

Goldberg, I. D. (1982) The endothelium: Injury and repair of the vascular wall, in: Kalsner, S. (ed) The Coronary Artery. Croom Helm, London, 15: 417–432.

Grotendorst, G. R., Seppa, H. E. J., Kleinman, H. K., et al. (1981) Attachment of smooth muscle cells to collagen and their migration toward platelet-derived growth factor. PNAS USA 78: 3669–3672.

Harris, J. R., Hellman, S., Henderson, I. C., and Kinne, D. W. (1987) Breast Diseases. J. B. Lippincott Co., Philadelphia.

Hynes, R. O. (1987) Integrins: A family of cell surface receptors. Cell 48: 549–554.

Lambert, R. A. (1916) Tissue cultures in the investigation of cancer. J. Cancer Res. 169–182.

Liotta, L. A., Thorgeinsson, U. P., and Gabisa, S. (1982) Role of collagenases in tumor cell invasion. Cancer Metast. Rev. 1: 277–288.

Liotta, L. A., Mandler, R., Murano, G., et al. (1986) Tumor cell autocrine motility factor. PNAS USA 83: 3302–3306.

Newgreen, D. F., and Eridson, C. A. (1986) The migration of neural crest cells. Int. Rev. Cytol. 103: 89–145.

Peyrieras, N., Hayfil, F., Louvard, D., et al. (1983) Uvomorulin: A nonintegral membrane protein of early mouse embryo. PNAS USA 80: 6274–6277.

Recamier, J. C. A. (1829) Recherches sur le Traitement du Cancer, par la Compression Methodique Simple ou Combinée et sur L'histoire Géréale de la Même Maladie, Vol. 2. Gabon, Paris.

Reidy, M. A., and Silver, M. (1985) Endothelial regeneration. VII. Lack of intimal proliferation after defined injury to rat aorta. Am. J. Pathol. 118(2): 173–177.

Rosen, E. M. and Goldberg, I. D. (1989) Protein factors which regulate cell motility. Invited Review, In Vitro Cell Dev. Biol. 25: 1079–1087.

Ruoslahti, E., and Pierschbacher, M. D. (1987) New perspectives in cell adhesion: RGD and integrins. Science 238: 491–497.

Schor, S. L., Grey, A. M., Picardo, M., Schor, A. M., Howell, A., Ellis, I., and Rushton, G. (1991) Heterogeneity amongst fibroblasts in the production of migration stimulating factor (MSF): Implications for cancer pathogenesis, in: Goldberg, I. D. (ed) Cell Motility Factors. Birkhauser Verlag, Switzerland, pp. 127–146.

Sholley, M. M., Gimbrone, M. A., Jr., and Cotran, R. S. (1977) Cellular migration and replication in endothelial regeneration: A study using irradiated endothelial cultures. Lab. Invest. 36: 18–25.

Wong, M. K., and Gottlieb, A. I. (1988) The reorganization of microfilaments, centrosomes, and microtubules during *in vitro* small wound reendothelialization. J. Cell Biol. 107: 1777–1783.

Yamada, K. M. (1983) Cell surface interactions with extracellular materials. Ann. Rev. Biochem. 12: 761–799.