FROM LOCAL INVASION TO METASTATIC CANCER
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FROM LOCAL INVASION TO METASTATIC CANCER

Involvement of Distant Sites Through the Lymphovascular System

Edited by

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Acknowledgements

We are grateful to the National Cancer Institute and NIH Office of the Rare Diseases for their support of the 2nd International Symposium on Cancer Metastasis and the Lymphovascular System: Basis for Rational Therapy being held in San Francisco, CA from May 2–5, 2007. We would like to thank the staff at Humana Press/Springer, Paul Dolgert, Frances Louie and Frank McGuckin, for their advice and expertise in making this book possible.
Foreword

This textbook captures the highlights of the timely symposium on cancer metastasis and the lymphovascular system. The symposium provided a unique forum for the convergence of biomedical research breakthroughs, presented by basic scientists, surgeons, radiologists, immunologists, and others, to address the central role of the lymphovascular system in the spread of cancer. The perspectives offered by experts in their respective fields of scientific inquiry inspired cross fertilization of ideas and paradigm-shifting hypotheses.

Regional lymph node metastasis is considered a prognostic indicator for the aggressive potential of solid tumors. However, despite recent advances in cancer biology and experimental therapeutics, critical gaps remain in our understanding of the molecular regulation of lymph node metastasis involving lymphatic invasion as a key feature. Lymphatic vascular biology has earned a prominent position in the field of cancer research, and lymphangiogenesis appears to be an attractive new target in the war against cancer.

The panel of experts assembled for the symposium reviewed the current status of basic, clinical and translational research in the field, including model systems to study lymphangiogenesis and angiogenesis; molecular imaging of lymph nodes; and therapeutic targeting of the lymphovascular system. The confluence of new knowledge and ideas was supported by a presentation on the vision of the National Cancer Institute. Perhaps no other time in the history of medicine has there been a strategic alignment of breakthroughs in biology, technology, and clinical research to advance the field in cancer metastasis and the lymphovascular system.
Preface

The aim of this book is to trace cancer metastasis from the primary sites to the regional lymph nodes and distant organs through the mechanism of local proliferation resulting in metastasis through the lymphovascular system. Rational therapy may be developed to curb the process of metastasis upon understanding these crucial steps of metastasis. Whether the cancer cells utilize the lymphatic or vascular channels or both to metastasize will be examined.

This book summarizes the 2nd International Symposium on Cancer Metastasis: Basis for Rational Therapy being held in San Francisco from May 3–5, 2007 by bringing together the basic scientists and clinicians to ask the central question of the role of the lymphovascular system in the spread of cancer. Thus, this book is able to link the bench to the bedside and vice versa in understanding the mechanisms of cancer metastasis.

In human solid cancers, the nodal status is the most important prognostic indicator for patients’ outcome. Recent developments in the sentinel lymph node (SLN) concept and technology have resulted in the application of such a procedure to define the first draining node or SLN as the primary gateway through which the cancer will spread.

Part I addresses several important developments in the biology and clinical aspects of cancer metastasis. Part II describes the relationship between tumor microenvironment and proliferation. Part III defines the process of lymphangiogenesis and angiogenesis with special reference to cancer metastasis. Part IV summarizes the development of multiple approaches in the imaging of cancer during its course of metastasis. Part V attempts to use the lymphatic system as a target to treat cancer. Part VI updates the latest cellular and molecular mechanisms of cancer metastasis. Part VII examines the role of molecular targeted therapy against growth factor receptors, signaling pathways and angiogenesis as therapeutic targets. Part VIII emphasizes the impact of tumor burden in the sentinel lymph nodes on the clinical outcome in several solid cancers. Part IX defines immune responses in the draining lymph nodes against cancer relating to immunotherapy against cancer. The role of cancer stem cells is being explored in Part X. With advent of molecular techniques, the genomic signatures of cancer may be developed and analyzed in Part XI. Parts XII and XIII summarize the therapeutic results of using new approaches in cancer treatment. Any promising leads from clinical trials in metastatic cancer may be used in the future as adjuvant therapies for occult metastatic deposits. Part XIV poses unanswered questions as future perspectives.

Perhaps, more uniquely, this book will bring the basic scientists, radiologists and clinicians together resulting in cross fertilization between these disciplines with intention to develop strategies to curb the process of metastasis.

San Francisco, CA

Stanley P. L. Leong, M.D.
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COLOR PLATE 1 Models of metastasis and gene expression profiles. Different theories of metastasis result in different outcomes with regard to gene expression profiles. In the conventional and stem cell models, a & b, the differential gene expression is thought to come from the specific mutations that lead to the development of cancer (black bars). In the conventional model (a), the mutated tumor cell gives rise to a cancer. A subsequent mutation, dark cell, confers metastatic ability. The differential gene expression profile of the metastasis reflects the genetic changes in the metastatic cell, which are now conferred to its progeny. In the stem cell theory of metastasis (b), the initial oncogenic mutation is responsible for alternations in gene expression. White cells are differentiated progeny of stem cell, but no further mutation is necessary to confer metastatic ability as it already exists in the cancer stem cell. Thus, no additional mutations are reflected in the gene expression profile. In the germline theory (c), the expression profile comes from the oncogenic mutations (black bar) as well as the genetic background (white). Regardless of what further oncogenic mutations, the genetic background of the host dominates the gene expression signature, leading to similar gene expression profiles in the primary and metastatic tumors. (Chapter 1, Fig. 2; see discussion on p. 6)

COLOR PLATE 2 Sentinel node with micrometastasis in gastric cancer. (Chapter 4, Fig. 1; see discussion on p. 30)

COLOR PLATE 3 Patterns of metastasis in sentinel nodes. a. Marginal sinus type, b. Intermediate sinus type, c. Parenchymal type, d. Diffuse type. (Chapter 4, Fig. 3; see discussion on p. 35)

COLOR PLATE 4 Proliferative activity of metastatic foci. a. Metastasis, b. Micrometastasis, c. Isolated tumor cell, d. Single cell. (Chapter 4, Fig. 4; see discussion on p. 38)

COLOR PLATE 5 Tracing of lymphatics of both hemi upper torsos (Male: A and C, Female: B and D) retrogradely from each first echelon lymph node colour coded. (Chapter 5, Fig. 8; see discussion on p. 51 and complete caption on p. 51)

COLOR PLATE 6 Signaling molecules possibly involved in tumor-induced lymphangiogenesis. In this figure, several growth factor and cytokine receptors and their
ligands are depicted that have been implicated in lymphangiogenesis and are expressed in the context of tumors. (Chapter 9, Fig. 1; see discussion on p. 97 and complete caption on p. 96)

COLOR PLATE 7  Tumor–vessel interactions: local and distant effects. Primary tumors secrete growth factors that can act locally on the lymphatics to increase vessel diameter and to increase the number of vessels. (Chapter 9, Fig. 2; see discussion on p. 98 and complete caption on p. 99)

COLOR PLATE 8  Chronological examination of 3D-CT LG (14). 3D-CT LG was examined 1, 3, and 5 min after iopamidol injection. Iopamidol flowed to extend over the SN into the next nodes. Five bead-like grouped lymph nodes in the axilla can be visualized by partially removing the pectoral muscle in the CT monitor. These are thought to be the order of lymph metastasis. Arrows point to lymph nodes 1–5 after SN. (Chapter 14, Fig. 3; see discussion on p. 164)

COLOR PLATE 9  Detection of SN metastasis (14). (a) Three SNs are recognized by 3D-CT LG. The right node drained from the main lymph duct was not metastasized. On the other hand, the other two nodes drained from the narrow collateral duct were metastasized. Dye and isotope could not reach as such the latter collateral nodes. These might become false-negative study. Therefore, 3D-CT LG is effective in raising accuracy of SNB. (b) The SN was metastasized, but the second node and the other nodes were all negative. (Chapter 14, Fig. 4; see discussion on p. 165)

COLOR PLATE 10  Image quality analysis using three different reconstruction softwares: filtering back projection (FBP), iterative reconstruction without attenuation correction (IRNC), and iterative reconstruction with attenuation correction (IRAC). White arrows: liver metastases nondetected by FBP reconstruction. (Chapter 15, Fig. 1; see discussion on p. 171)

COLOR PLATE 11  SRS whole-body scan (left) in a patient with metastatic thymic neuroendocrine tumor demonstrated several foci of increased 111In-pentetreotide uptake in the chest, and right upper and lower abdomen. Selected coronal and sagittal SPET/CT slices showed the precise localization of one of the areas of abnormal uptake in the right lower abdomen (A) and in the right upper abdomen (B). Fused images (right) enabled metastatic lesions. (Chapter 15, Fig. 2; see discussion on p. 173)

COLOR PLATE 12  Lymphotropic properties of Ad. A transmission electron micrograph image of human adenoviruses depicting the icosahedron-shaped viral particles (a). Alexa fluor-555 labeled AdTSTA-FL virus was injected into the forepaw of severe combined immunodeficiency (SCID) mice and confocal images of lymph node (LN) sections taken at 1 or 24 hours after viral injection revealed the presence of fluorescent virus in the draining axillary node (b). Functional lymphatic drainage of adenovirus from the forepaw (c) or the subcutaneous (s.c.) chest site (d) to the ipsilateral draining LN can be detected by bioluminescent luciferase
signals. $1 \times 10^7$ infectious units of constitutive CMV promoter-driven virus (Ad–CMV–FL) were injected into the nontumor-bearing SCID mice. (Chapter 16, Fig. 1; see discussion on p. 181)

COLOR PLATE 13 Prostate-specific TSTA system and imaging reporter Ad. A schematic representation of the two-step transcriptional amplification (TSTA) system (a). The AdTSTA-FL and the luciferase bioluminescent signals produced by this Ad after intratumoral injection as imaged by luciferin-based bioluminescence imaging (BLI) (b). AdTSTA-sr39tk PET-imaging reporter vector and the $^{18}$F-FHBG signal produced after intratumoral vector injection (c). PSE-BC = chimeric PSA enhancer/promoter; GAL4/VP2 = Fusion of the yeast GAL4 DNA-binding domain and two copies of the herpes simplex virus VP16 activation domain; TATA = TATA box; 5 × GAL4 = 5 GAL4-binding sites; and HSV1-sr39tk = mutant herpes simplex virus type 1 thymidine kinase. (Chapter 16, Fig. 2; see discussion on p. 181)

COLOR PLATE 14 Functional imaging of LN metastasis. Bioluminescence imaging of a male SCID mouse bearing LAPC-9 prostate tumor on left upper back (a). BLI was performed 4 days after injecting $1 \times 10^7$ infectious units of AdTSTA-FL into the left paw. Histological confirmation of metastatic prostate tumor cells in the LN by H&E (left, 10×) and anticytokeratin staining (right, 40×) (b). Transverse and coronal sections of $^{18}$F-FHBG PET from another LN-positive mouse scanned 4 days after injecting $1 \times 10^8$ infectious units of AdTSTA-sr39tk into the left paw (e). Photograph of enlarged brachial and axillary LNs (d). (Chapter 16, Fig. 3; see discussion on p. 181)

COLOR PLATE 15 (A) Malignant melanoma of the heel with popliteal SLN metastasis. (B) The cancer cells reach the regional nodes by “embolization” (arrows) rather than by centripetal permeation, discontinuous embolism (10,22,62,93). (C) Arrow indicates metastatic embolus. (Chapter 30, Fig. 1; see discussion on p. 351)

COLOR PLATE 16 (A) Lymphangiogram showing the lymphatic drainage of the right testicle (AP view) (dog injection). (B) Lateral view. Direct lymphangiogram of the testicle disclose the SLN in the precaval area (dog). (C) Bilateral direct testicular lymphangiogram in human concomitant with dorsum of the foot injection. The arrows indicate the location of the SLN in the right side as well as the left. (Chapter 30, Fig. 2; see discussion on p. 351)

COLOR PLATE 17 (A) Arrows indicate SLN harboring metastasis (lateral view). (B) Arrows indicate SLN metastasis (AP view). (C) Surgical specimen of retroperitoneal lymph node dissection. Arrows indicate SLN. (Chapter 30, Fig. 3; see discussion on p. 351)

COLOR PLATE 18 (A) Advanced malignant neoplasia of the testicle (reluctant patient). (B) Metastasis lymph nodes pre-aorta–cava area. (C) SLN of the testicle harboring metastasis. (Chapter 30, Fig. 4; see discussion on p. 351)
COLOR PLATE 19  Lymphazurin 1% is being injected in the subserosal layer of right colon.  (Chapter 31, Fig. 1; see discussion on p. 366)

COLOR PLATE 20  Blue lymphatic traveling to a blue sentinel lymph node (arrow) seen on the retroperitoneal surface. (Chapter 31, Fig. 2; see discussion on p. 366)

COLOR PLATE 21  Fluorescent lymphatic reaching a fluorescent sentinel lymph node (arrow) seen in a dark room with Wood’s Light illumination. (Chapter 31, Fig. 3; see discussion on p. 368)

COLOR PLATE 22  IHC staining with antibody to S-100 demonstrates significant reduction in IDC area and density in SN versus non-SN (NSN). T cell (CD43) area was also reduced in SN compared to non-SN while B cell (CD20) area was not altered. The presence (SN +) or absence (SN –) of metastases to the SN did not appear to alter the differences in IDC area or density. (Chapter 35, Fig. 1; see discussion on p. 413)

COLOR PLATE 23  Sample amplification plot for GAPDH standards demonstrating the threshold cycle ($C_t$) for each of the serial dilutions. In the second graph, the $C_t$’s are plotted against the Log(quantity—C0), providing a standard line with a slope and quality of fit. (Chapter 35, Fig. 5; see discussion on p. 416)

COLOR PLATE 24  Significant difference in cytokine gene expression in the SN compared to the NSN (non-SN). The relative patterns of cytokine expression are reversed in the presence or in absence of residual melanoma found during LM/SL. Presence of residual tumor significantly increases the levels of cytokine expression in the SN. Most dramatic increase is noted in the expression of IDO, which is an enzyme expressed in immune downregulatory dendritic cells (56,57). (Chapter 35, Fig. 6; see discussion on p. 417)

COLOR PLATE 25  Real-time quantitative PCR amplification plot for GAPDH, a standard housekeeping gene is shown. The RNA was extracted from an archival tissue that was fixed in formalin and embedded in paraffin. The figure demonstrates successful quantitative measurement of GAPDH gene expression in such tissue sample. (Chapter 35, Fig. 7; see discussion on p. 419)

COLOR PLATE 26  Relative T cell and B cell area and IDC density in SN based on preoperative dose of GM-CSF. Patients receiving GM-CSF 150 $\mu$g/m$^2$ appeared to have the greatest morphologic change to the SN. (Chapter 35, Fig. 9; see discussion on p. 420)

COLOR PLATE 27  Association between Br-CSC gene expression profiles and prognosis of breast cancer patients. A Pearson correlation coefficient was calculated for the correlation between a gene signature obtained from Br-CSCs (the “invasiveness gene signature” or IGS) and each of the 295 tumors included in a publicly available breast cancer patient database (the
Netherlands Cancer Institute database) on the basis of the expression values of the 186 genes that are included in the gene signature. Patients were separated into two groups according to the correlation values, with 0 used as the threshold. Kaplan–Meier survival curves for the two groups were compared, with overall survival (Panel A) and metastasis-free survival (Panel B) as the clinical end points. Patients with tumors with a gene expression pattern that was similar to the IGS (correlation coefficient, >0) had worse outcomes than those with tumors with a gene expression pattern that was not similar to the IGS (correlation coefficient, ≤0). Reproduced with permission from Liu et al., *N Engl J Med*, 2007; 356:217–226. Copyright © 2007 Massachusetts Medical Society. All rights reserved. (Chapter 38, Fig. 1; see discussion on p. 446)

COLOR PLATE 28 Metastasis-free survival of breast cancer patients after stratification based on the combined use of the IGS and the WR signature. A Pearson correlation coefficient was calculated for the correlation between each of the two signatures (IGS and WR) and each of the 295 tumors included in the Netherlands Cancer Institute database. Group 1 included patients with a negative correlation to both the IGS and the WR signature. Group 2 included patients with a positive correlation to either the IGS or the WR signature. Group 3 included patients with a positive correlation to both the IGS and the WR signature. The 10-year metastasis-free survival of the three groups was 80, 69, and 47%, respectively. Reproduced with permission from Liu et al., *N Engl J Med*, 2007; 356:217–226. Copyright © 2007 Massachusetts Medical Society. All rights reserved. (Chapter 38, Fig. 2; see discussion on p. 446)

COLOR PLATE 29 Comparison of ER antibodies SP1 and 1D5. The SP1+/1D5– cases have cumulative survival at 10 years similar to those of SP1+/1D5+ tumors (6). (Chapter 40, Fig. 5; see discussion on p. 472)

COLOR PLATE 30 This is an example of the hybridization of reference DNA (green) and tumor DNA (red) to an interphase spread of chromosomes (ready for mitosis and frozen by adding colchicine to stop spindle apparatus). Above the red line shows amplification of tumor gene copy and below the green line shows loss of gene copy number. (Chapter 40, Fig. 9; see discussion on p. 478)

COLOR PLATE 31 QRT-PRC. The RNA is extracted, reverse transcribed and mixed with two specific primers (generally within 100 bp of each other in the case of formalin-fixed tissue) and a fluorescently labeled probe specific for the same target. The probe has both a fluorescent reporter attached to one end, and a quencher on the other—this quenches the fluorescent signal. The primers and probe anneal to the specific target gene. Due to the 5'-exonuclease activity of the Taq polymerase, already-bound fluorescent-labeled probe is degraded while new PCR product is being synthesized. This process releases the fluorescent tag from the quencher and generates a fluorescence signal that is directly proportional to the amount
of PCR product in the tube. This signal can be quantitated and the amount of mRNA determined. (Chapter 40, Fig. 10; see discussion on p. 479)

COLOR PLATE 32 Gene expression patterns of 85 experimental samples representing 78 carcinomas, three benign tumors, and four normal tissues, analyzed by hierarchical clustering. The closer samples are together, the more similar are their expression profiles. The tumor specimens were divided into six subtypes based on differences in gene expression. Note differences in ER− and ER+. The cluster dendrogram shows the six subtypes of tumors from left to right (colored as): basal-like, red; ERBB21, pink; normal breast-like, green; luminal subtype C, light blue; luminal subtype B, yellow; luminal subtype A, dark blue.(57). (Chapter 40, Fig. 11; see discussion on p. 481)

COLOR PLATE 33 Individual dendrogram branches are colored according to the strongest correlation of the corresponding tumor with the subtype centroid as defined for the Perou/Sorlie samples. The best discrimination was between the tumors of the luminal A cluster at high levels and tumors that exhibited expression profiles characteristic of the basal, HER2 or luminal B subtypes. The strongest correlation was with the basal subtype (red branches)—all of which are contained within the left branch of the dendrogram in a tight cluster. (Chapter 40, Fig. 12; see discussion on p. 481)

COLOR PLATE 34 Kaplan-Meier analysis of disease outcome in two patient cohorts. (A) time to development of distant metastasis in the 97 cases from van ‘t Veer et al. Patients were stratified according to the subtypes as shown in Fig. 14. (B) Overall survival for 72 patients with locally advanced breast cancer in the Norway cohort. The normal-like tumor subgroup was omitted in both analyses. (Chapter 40, Fig. 13; see discussion on p. 482)

COLOR PLATE 35 Supervised classification on prognosis signatures. (A) Prognostic reporter genes identify optimally two types of disease outcome from 78 sporadic breast tumors into a poor prognosis and good prognosis group. Each row represents a tumor and each column a gene. Genes are ordered according to their correlation coefficient with the two prognostic groups. The solid line represents the prognostic classifier with optimal accuracy; dashed line with optimized sensitivity. Above the dashed line are patients with a good prognosis and below those with a poor prognosis. The metastasis status for each patient is shown in the right panel: white indicates patients with metastases within 5 years and black indicates those disease free for at least 5 years. (Chapter 40, Fig. 14; see discussion on p. 485)

COLOR PLATE 36 Kaplan–Meier analysis of the probability that patient would remain free of distant metastases and the probability of overall survival among all patients. (Chapter 40, Fig. 15; see discussion on p. 487)
COLOR PLATE 37 Kaplan–Meier analysis of the probability that lymph node-negative patient (left two panels) and lymph node-positive patients (right two panels) would remain free of distant metastases and the probability of OS, respectively. (Chapter 40, Fig. 16; see discussion on p. 487)

COLOR PLATE 38 The recurrence score (RS) is used to predict patient prognosis, it ranges from 0 to 100 and it is divided into three risk groups: (1) a low-risk score correlating with a low risk of distant recurrence, RS 0–18; (2) an intermediate risk score correlating with an intermediate risk of distant recurrence, 18 < RS < 31; and (3) a high-risk score correlating with a high risk of distant recurrence, RS ≥ 31. (Chapter 40, Fig. 17; see discussion on p. 490)

COLOR PLATE 39 Microarray analysis of the radial and vertical growth phases within a single, large, primary melanoma. Note that in the vertical growth phase, there is a predominance of green signals, indicating losses of gene expression. (Chapter 41, Fig. 2; see discussion on p. 500)

COLOR PLATE 40 Representative primary melanoma with evaluable radial and vertical growth phases immunostained for MMP-10 (a) and CDH3 (b). Prominent staining is noted within the radial growth phase consistent with gene profile analysis showing a loss of these genes in the vertical growth phase. (Chapter 41, Fig. 3; see discussion on p. 501)

COLOR PLATE 41 Immunohistochemical staining for a patient with a melanoma in situ with extensive regression. The radial growth phase markers, CDH3 and MMP-10, were detected in both the primary melanoma and in the metastasis. (Chapter 41, Fig. 4; see discussion on p. 502)

COLOR PLATE 42 Unsupervised hierarchial clustering of metastatic melanoma defines subtypes I and II. (Chapter 41, Fig. 5; see discussion on p. 502)

COLOR PLATE 43 Microanalysis is able to distinguish nevi from melanoma. (Chapter 41, Fig. 6; see discussion on p. 503)

COLOR PLATE 44 Primary melanoma to metastasis: radial growth phase melanomas have the potential to metastasize and the development of a vertical growth phase may not be a prerequisite for the development of metastatic disease. (Chapter 41, Fig. 7; see discussion on p. 506)

COLOR PLATE 45 Interferon (IFN) signal transduction. IFNs bind to specific receptors and induce tyrosine phosphorylation of receptors by JAK kinases providing a docking site for the STAT proteins which are subsequently phosphorylated by the Jak kinases. Activated STAT proteins dimerize and translocate into the nucleus in order to directly bind to specific DNA sequences as transcription factors (from [11]). (Chapter 46, Fig. 1; see discussion on p. 556)
COLOR PLATE 46 Typical papular rash in a patient treated with sorafenib. (Chapter 47, Fig. 1; see discussion on p. 567)

COLOR PLATE 47 Typical hyperkeratotic hand–foot syndrome in a patient treated with sorafenib. (Chapter 47, Fig. 2; see discussion on p. 567)