

Preface

Skeletal cancers may originate in bone as primary tumors, or arrive there as a consequence of the metastatic dissemination of cancer cells from distant sites, giving rise to secondary or tertiary tumors. Progression of malignant cancers in bone is fostered by the multipotential bone marrow stromal cells and the complex cellular milieu to which they give rise, including osteoblasts, osteoclasts, hematopoietic stem cells, bone marrow endothelial cells, and their precursors. Changes in genotype and phenotype enhance tumorigenicity of cancer cells in bone, as they adapt to and remodel the bone marrow microenvironment. Because cultured bone cells that have been in contact with cancer cells for extended time periods can transform non-tumorigenic cells, it is apparent that bone cells undergo phenotypic and genotypic alterations during skeletal cancer progression. Components of the complex bone microenvironment contribute significantly to the growth and proliferation not only of primary cancers, such as osteosarcoma or myeloma, but also to the process of metastasis of epithelial-derived cancers such as prostate or breast cancer.

Bone and Cancer, as have previous volumes of *Topics in Bone Biology*, deals with the basic science, translational, and clinical aspects of bone and, in this case, the relationship to cancer. Written by authorities, the chapters discuss background and history, proceeding to the questions of the day, with emphasis on what yet is to be learned. The material is of interest to medical, dental and graduate students, resident physicians and dentists, bone researchers, and all those concerned with understanding how bone attracts and becomes home to so many cancers.

Aaron M. Havens, Yusuke Shiozawa, and Russell S. Taichman, in Chapter 1, discuss in detail the relationship between hematopoiesis and the bone marrow niche in which hematopoietic stem cells and early hematopoietic progenitor cells differentiate. The niche integrates changes in nutrients, oxygen, and in paracrine and autocrine signals that in turn alter the rate of cell multiplication. The niche is also the site to which metastasizing cancer cells are attracted and where they multiply. The chapter discusses in cellular and molecular terms how osteoblast surfaces, which effectively create a niche, play a role in hematopoiesis. Discussion then proceeds to vascular and marrow niches, the still largely unknown role of adipocytes, of reticular cells, and to the concept of cells homing to bone during fetal life and in many cancers.

The genetics of osteosarcoma, a relatively rare primary bone tumor, are discussed by Marc F. Hansen in Chapter 2. After describing the histopathology of osteosarcoma, Hansen describes unconventional subtypes, as well as the more common sarcoma of head and neck. He then proceeds to analyze the inherited predisposition to osteosarcoma. The Li-Fraumeni syndrome is discussed, as is the Rothmund-Thompson syndrome, and the relationship to Paget's disease. The remainder of the chapter is devoted to an analysis of the genetics of osteosarcoma, along with a detailed discussion of the role of genes like RB1, TP53, the role of the Wnt signaling pathway, genomic stability, and chromosomal instability. Like most chapters, Chapter 2 is extensively referenced.

In Chapter 3, Rajesh Sehgal, Kristen M. Sanfilippo, and G. David Roodman discuss multiple myeloma, the most common hematologic malignancy in adults. After describing the pathophysiology of bone disease in multiple myeloma, the authors discuss the role of osteoclast activation and of RANKL and MIP-1 α in increasing osteoclastogenesis, of PTHrP as the major mediator of hypercalcemia, and of IL-6 acting to stimulate osteoclast formation and of IL-7, IL-3, and DKK1 in inhibiting osteoblast activity, differentiation, and preosteoblasts. The chapter then describes the clinical manifestations of myeloma, including bone destruction, hypercalcemia, neurologic, and other systemic complications. Diagnosis, prognosis, and treatment are evaluated. The chapter also discusses Hodgkin's disease, non-Hodgkin's lymphoma, and adult cell leukemia/lymphoma, and their involvement in bone. This chapter, like many, has pertinent illustrations.

The role of the bone marrow endothelium in cancer metastasis is discussed in Chapter 4, by Carlton R. Cooper, Robert A. Satcher, Lisa A. Gurski, and Kenneth L. van Golen. Bone pain, pathologic fractures, spinal cord compression – termed skeletal-related events – are the result of cancer cells metastasizing to bone, a process brought about by bone marrow endothelial cells that promote entry into the bone marrow and lead to cancer growth. The authors describe the natural history of bone cancer, its prognosis and clinical course, proceeding to an overview of endothelial cells and their role in bone physiology and tumor angiogenesis. The components of the metastatic phenotype are then discussed, with reference to the Rho GTases, their role in angiogenesis and endothelial cell motility. On the basis of their own findings, the authors conclude that information on one cell type, e.g., HUVEC, cannot be extrapolated to other cell types, e.g., BMEC. Therefore, therapeutic approaches targeting BMEC cannot be based on findings with HUVEC. Several tables enhance the value of this chapter.

The role of lysophosphatidic acid in bone physiology and bone cancer has been clarified only in recent years. Olivier Peyruchaud and Norman J. Karin, in Chapter 5, describe this molecule, its major *in vivo* source, its biological activities, its receptors, its expression in bone cells, and its rapid effects on bone and cartilage cells. These include calcium signaling, MAP kinase activation, and rearrangements of the cytoskeleton. Long-term effects of lysophosphatidic acid are on cell proliferation, survival, and differentiation. The cytoskeleton is also rearranged so as to permit cell movement to take place. As yet little is known about how lysophosphatidic acid affects gene expression. In fracture healing, lysophosphatidic acid may modulate proliferation and

migration of osteoblast progenitor cells to the fracture gap. Evidence is cited to the effect that this molecule may foster arthritis progression and that its receptor is expressed in thyroid and prostate cancer cells. Lysophosphatidic acid may also play a role in cancer progression, inasmuch as silencing the molecule reduces disease progression.

The important role the bone microenvironment plays in siting metastasizing cancer cells is dealt with in Chapter 6, by Anna Podolanczuk, Bethan Psaila, and David Lyden. They discuss specific tumor growth factors like the vascular endothelial growth factors that modulate angiogenesis, the fibroblast growth factor that upregulates fibronectin expression and which in turn provides an adherence platform for metastasizing cancer cells. Blocking these factors may slow cancer progression and several such pharmaceutical inhibitors are discussed. An important chemokine that governs migration patterns of hematopoietic cells is CXCL12, also important for metastasis, as are angiopoietin and osteopontin, which retain stem cells in the niche. The authors discuss in detail the role of bone marrow-derived cells for supporting tumor cell survival, promoting their dissemination and migration, and their role in building the niche. Genetic regulation and targeting of metastasis is dealt with toward the end of the chapter.

In Chapter 7, Sabine Riethdorf, Volkmar Müller, Catherine Alix-Panabières, and Klaus Pantel provide information on methods for detecting and characterizing disseminated tumor cells in the bone marrow of cancer patients. They list advantages and disadvantages of the various immunocytochemical and molecular assays of these cells and discuss the significance of detecting them in the bone marrow of patients who have no signs of clinical metastasis. The assays therefore may have prognostic value. In addition, characterization of these relatively few disseminated cells may help define the process of early tumor cell dissemination and therefore help identify novel therapeutic targets.

Inna Serganova and Ronald G. Blasberg, in Chapter 8, analyze and discuss molecular imaging of cancer cells in bone. The most widely used imaging modalities are optical fluorescence, bioluminescence, photon and single photon emission tomography, autoradiography, gamma camera, magnetic resonance spectroscopy, diffusion-weighted imaging, ultrasound, and computed tomography. These techniques are described and analyzed. The chapter then proceeds to a discussion of genes encoding receptors, with emphasis on the somatostatin receptors. Imaging of cancer cells in bone by scintigraphy, magnetic resonance imaging, and positron emission tomography is described, as is application to mouse models; the limitations or advantages of each method are evaluated. The chapter concludes by indicating two areas in bone cancer research that need development, namely appropriate animal models and multi-modality imaging strategies.

In Chapter 9, Larry J. Suva, Richard W. Nicholas, and Dana Gaddy discuss the cytokines and chemokines, signaling molecules that link inflammatory responses with cancer development. Tumors develop in a microenvironment that is predominantly managed by inflammatory cells and that plays a critical role for cancer progression. The chapter discusses the relationship between this microenvironment, the cells in that micromilieu, and the cytokines that stimulate metastases to tumor

progression in bone. They include TNF- α , the interleukins (6, 8, 10, 12, 23), (CXCL12/CXCR4), and TGF- β . Their specific targets and whether they act to promote or inhibit a particular process are discussed in detail. The authors conclude by urging the study of the integrated response of cells within the secreted components in the bone marrow microenvironment.

In Chapter 10, Leland W.K. Chung, John A. Petros, and Mary C. Farach-Carson take on the complex subject of osteomimicry that occurs during bone metastasis of many cancers. The authors introduce the concept of osteomimicry and of some unique signaling phenomena that occur during the processes of osteomimicry to create a signaling triad that is associated with poor prognosis. They also describe the plasticity of cancer cells and speculate on the evolutionary significance of cancer cell differentiation. Particular attention is paid to the important role of the cancer-cell-derived receptor activator, NF κ B ligand (RANKL), which can increase bone turnover and ultimately facilitate cancer growth and survival in bone. Finally, the authors speculate on how osteomimicry supports signal amplification leading to cancer progression. Prostate cancer osteomimicry in the bone niche is used to illustrate how the understanding of the molecular signaling cascade of osteomimicry may help diagnosis, prediction of progression, and therapy of prostate cancer metastases.

Bone pain is the most common pain of cancer patients. Patrick W. O'Donnell, Nancy M. Luger, and Denis R. Clohisey address this question in Chapter 11, dealing also with the fractures that cancer patients experience as a result of metastatic disease from osteolytic cancers such as myeloma or breast cancer. They discuss bone pain treatment by radiation, radiofrequency tumor ablation, and the use of radiopharmaceuticals. To be able to test therapeutic approaches to bone pain, animal models are needed and discussed, as are various therapeutics and their effect on remodeling. The authors conclude that the mainstay of treatment of bone cancer pain is opioid analgesia, but there is a need for combined therapies that target the multiple mechanisms that drive bone pain.

In Chapter 12, David J. DeGraff, Fayth L. Miles, Ronald R. Gomes, and Robert A. Sikes discuss in detail small animal models for the study of the various cancers in bone. They deal with the four routes of xenograft administration, orthotopic, intracardiac, intravenous, and intrafemoral/intratibial, in each of the animal models of cancer in breast, lung, prostate, and kidney, and in models of multiple myeloma and melanoma. They also take up, where appropriate, transgenic and syngeneic approaches, the SCID mouse model into which human bone tissue is injected, and the occasional spontaneous animal cancer that is a model for a human cancer. In concluding, the chapter calls attention to the need to model metastasis.

Hormonal and bisphosphonate therapies have been used in many bone cancers. Pamela Taxel and Faryal S. Mirza, in Chapter 13, deal in detail with these therapies in prostate and breast cancer. Hypogonadism is a result of treatment with gonadotropin-releasing agonists, estrogen or orchidectomy. Taxel and Mirza deal with the consequences of this situation, as well as treatment of men in their eighties who often are hypogonadic. Hypogonadism constitutes a major risk factor for osteoporosis. It requires treatment that diminishes the rate of bone mass loss and the likelihood of a

pathologic fracture. An interesting consequence of hypogonadism is the simultaneous loss of estrogen, with the result that bone mass loss is further amplified. In their analysis of treating breast cancer, the authors deal with tamoxifen and its effect in lowering osteoporotic fractures, and with the aromatase inhibitors, which cause a significant lowering of estradiol levels in postmenopausal women, therefore raising the rate of bone loss and risk of fractures. They compare treatment with the aromatase inhibitors, anastrozole, letrozole, and exemestane, and with tamoxifen, on a short-term and long-term basis. The chapter then proceeds to a detailed evaluation of bisphosphonates in the treatment of prostate and bone cancer and to an examination of the prevention of bone loss with specific bisphosphonates, including zoledronic acid. The chapter concludes with a call to treat even moderate osteopenia in patients with breast or prostate cancer and, if initially there is no sign of osteopenia, to do periodic tests of bone turnover and bone mineral density to be able to intervene early if bone turnover remains high or bone mineral begins to decrease.

Chapter 13 discusses treatment of bone cancer due to metastasizing prostate or breast cancer. Chapter 14, by Charles J. Schneider and Stephen S. Grubbs, analyzes therapeutic approaches to kidney, thyroid, and lung cancer. Patients with renal cell carcinoma often have multidrug resistance and in the past were treated with immunotherapy. The chapter discusses newer targeted therapies such as monoclonal antibodies against IL-6 or TNF- α , anti-angiogenic drugs, or Raf kinase inhibitors. In the discussion of thyroid cancer, the authors distinguish between well-differentiated carcinoma, medullary thyroid carcinoma, anaplastic carcinoma, and actual or potential treatment for these conditions. Almost half of lung cancer patients develop bone cancer. The addition of bevacizumab to carboplatin and paclitaxel, approved by the Food and Drug Administration (USA) in 2006, has led to somewhat longer survival for lung cancer patients and available results are evaluated. The chapter also adds to the discussion of available treatment of breast and prostate cancer.

In 1957 Thomas treated two patients with advanced leukemia with infusions of marrow from their identical twins after they had received high-level radiation. This led to the use of allogeneic transplants in combination with radiation. In Chapter 15, Jose Francisco Tomas and Sergio A. Giralt describe and analyze hematopoietic transplants in patients with a genetic disorder, malignancy, or an intrinsic bone marrow disorder. They distinguish between allogeneic, syngeneic, and autologous transplants, describe treatments that involve radiation or chemotherapy, as applied to acute lymphoblastic leukemia, chronic myeloid leukemia, or the myelodysplastic syndrome. The chapter also discusses Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia. Transplant-related complications are evaluated. The chapter concludes that although allogeneic stem cell therapy has cured a variety of hematological malignancies, complications related to graft-vs.-host diseases and disease recurrence remain major barriers.

The spine is the most common site for cancer that localizes in bone. Chapter 16, by Marsha L. Haley, Peter C. Gerszten, and Steven A. Burton, focuses on stereotactic radiosurgery as therapy for metastatic disease of the spine. The authors review the history of external beam radiation ther-

apy, including the evolution of radiosurgery, the amount of dose that can be delivered, with the radiosensitivity of the adjoining soft tissue the limiting factor. Because radiation therapy provides palliation in a significant majority of patients, radiation oncologists are consulted for evaluation of patients and the chapter provides guidance on how to evaluate patients and to devise optimum radiation dosage. Proper dosage depends on accurate localization of the tumor and the chapter discusses how to achieve that and full target immobilization. It also discusses stereotactic radiotherapy, as a compromise between radiotherapy and stereotactic radiosurgery. The chapter concludes by pointing out that radiosurgery has become an inter-speciality because orthopedic and neurosurgeons have become members of the radiation oncology team. This in turn has led to advances and greater potential for new technology.

This volume is the outcome of clinicians from several specialties joining with scientists of diverse orientation. It thus illustrates the need and desirability for a multiple and diverse focus on a disease that still is the most common cause of death. We thank the authors for their dedication and their willingness to let their contributions become part of a larger, integrated whole. Our thanks go to Springer, publishers of the series, for their help in assuring quality and in producing a handsome volume. We dedicate this volume to the many victims of what as yet remains a dreaded disease.

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Bone and Cancer

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2009, X, 246 p. 63 illus., 35 illus. in color., Hardcover

ISBN: 978-1-84882-018-0