The Tumor Microenvironment 4
Series Editor: Isaac Witz

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Tumor-Associated Fibroblasts and their Matrix

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Tumor-Associated Fibroblasts and their Matrix

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ISBN 978-94-007-0658-3 e-ISBN 978-94-007-0659-0
DOI 10.1007/978-94-007-0659-0
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2011925928

Cover design: deblik, Berlin

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

During the last century cancer research was mainly focussed on the tumor cells alone which could be easily propagated in cell culture. During this time many important findings were obtained clearly demonstrating that cancer is a genetic disease, controlled by the activation and/or inactivation of critical control genes.

However during the last two decades it has become increasingly clear that genetic alterations alone are not the sole driving force behind tumor development but that tumor growth and progression are rather intimately controlled by the microenvironment. One could almost speak of are "rediscovery" of the tumor as a highly complex tissue composed of carcinoma cells and surrounding stroma. Studies in different areas of biology including tumour biology have demonstrated that tissue structure, function and dysfunction are highly intertwined with the microenvironment and that during the development of cancer tissue biology and host physiology are subverted to drive malignant progression. It is now clear that the context is crucial and that the status of the cellular microenvironment plays a significant role in determining whether cells within a tissue retain their normal architecture or undergo tumor progression.

The tumor stroma or microenvironment is made up of multiple non-malignant cell populations, including fibroblasts, adipocytes, endothelial and inflammatory cells that are embedded in a tumour specific extracellular matrix (ECM). Nowadays, there is a huge interest in tumor stroma research, and in understanding the contributions of the different stromal cell types to tumor growth and progression. One of the key components of the tumor microenvironment in carcinomas are activated fibroblasts termed cancer associated fibroblasts (CAFs). In the meantime our knowledge of CAFs has changed from being viewed as a passive bystander to becoming an important co-mediator of cancer progression.

In response to cancer growth, host stromal fibroblasts undergo a dramatic morphologic and biochemical transition to form "reactive stroma" in a desmoplastic reaction much like the granulation tissues found at the site of wound healing. While the malignant cells activate fibroblasts in the tumor stroma by various stimuli, including growth factors and cytokines, cancer associated fibroblasts secrete growth factors and build a permissive soil in which the cancer cells thrive. CAFs are responsible for the elaboration of most of the connective tissue and ECM components

as well as, proteolytic enzymes and their inhibitors. The composition and structure of the ECM in the tumor microenvironment is essential for promoting tumor development and metastasis. The constituents of the ECM include collagens, laminins, fibronectin and several proteoglycans. They provide mechanical support for cells, facilitate cell communication and serve as substrates for cell migration. Changes in the composition or architecture of the extracellular matrix within tumors can alter integrin expression and function and promote metastatic progression, angiogenesis and lymphangiogenesis.

In this unique textbook world leading experts of the area of tumor microenvironment review the most recent knowledge of the still growing complexity of the tumor microenvironment focussing on tumor associated stromal cells and the most important extracellular matrix components and summarize the role of these players in tumor progression. Moreover, novel therapeutic targets are discussed that have been discovered in the tumor microenvironment and are increasingly used in experimental and clinical tumor therapy. The message from their contributions is clear: the tumor microenvironment and its components are important and essential players in tumor progression and interesting targets for novel therapeutic strategies. However there are still many white areas on the map and we are just beginning to understand the complex interplay between tumor and stromal cells.

We express our deepest gratitude to all our colleagues who have made this book the first comprehensive antology covering all major aspects of the role of the tumor microenvironment and its extracellular matrix components.

Heidelberg Margareta M. Mueller and Norbert E. Fusenig

Contents

Part VI Therapeutic Application/Targeting

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Part I
The Tumor Microenvironment

Chapter 1
Critical Roles of Stromal Fibroblasts in the Cancer Microenvironments

Leland W. K. Chung

1.1 Introduction

A mounting body of evidence suggests that the ability of cancer cells to interact reciprocally with the host microenvironment contributes to cancer growth, progression and resistance to therapeutic interventions. Interactions with stromal fibroblasts at the primary site and marrow stromal cells at metastatic sites could create a favorable microenvironment supporting cancer growth, survival, evasion of immune surveillance and resistance to therapy (Mueller and Fusenig 2004; Chantrain et al. 2008; Karnoub et al. 2007; Ronnov-Jessen and Bissell 2009; Chung et al. 2006). Changes in cancer microenvironments could also add selection pressures favorable to cancer cell evolution, increasing cancer cell heterogeneity and reciprocally causing the co-evolution of adjacent stromal fibroblasts, resulting in the development of organ- and stage-specific stromal fibroblasts capable of programming and reprogramming the fate of cancer cells (Hill et al. 2005; Sung et al. 2008; Franco et al. 2010). Over the past several years, active research has broadened our awareness of the plasticity of cancer-associated stroma, which undergo both morphologic and functional transitions supporting the pathogenesis of cancer cells (Sung et al. 2008). The dynamic presence of bone marrow-derived mesenchymal stem cells in localized and metastatic cancers contributes further to the diversity and heterogeneity of cancer-associated stroma and ultimately determines the site of cancer metastasis, while stromal fibroblasts have multiple functional roles modulating cancer growth either positively or negatively (Martin et al. 2010; Molloy et al. 2009; Rhodes et al. 2009; Zhao et al. 2009a). Figure 1.1 depicts how soluble factors, insoluble extracellular matrix proteins, and reactive oxygen species secreted by cancer cells and cells in cancer microenvironments can guide and maintain the growth and differentiation of local and distant cancers and their interactions with host microenvironments

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M. M. Mueller, N. E. Fusenig (eds.), *Tumor-Associated Fibroblasts and their Matrix,* The Tumor Microenvironment 4, DOI 10.1007/978-94-007-0659-0_1,

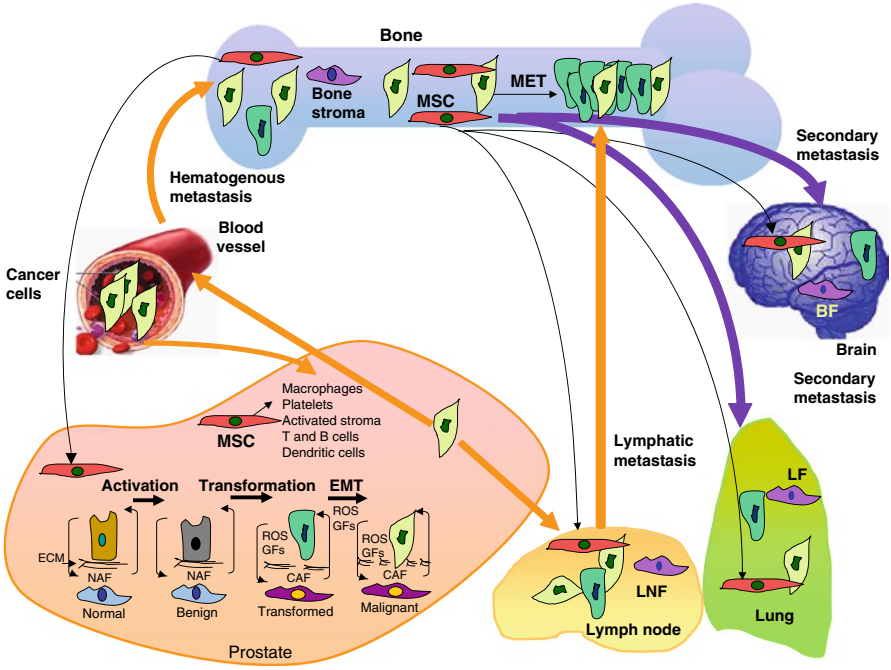

Fig. 1.1 Tumor-microenvironments interactions contribute to prostate cancer skeletal and soft tissue metastases. At the primary site, reciprocal cellular interactions between prostate cancer cells and local/migrating stromal fibroblasts, mediated by soluble and insoluble factors and ROS, promote the transition of normal/benign stromal fibroblasts to cancer-associated stromal fibroblasts which activate and transform prostate epithelial cells to gain increased growth and survival potential. Subsequently, through epithelial-to-mesenchymal transition (EMT), prostate cancer cells gain futher growth, survival, migratory, invasive and metastatic potential allowing them to metastasize to the skeleton via hematogeneous routes. Prostate cancer cells also frequently metastasize to lymph node and then reach the skeleton through lymphatic metastatic routes. Metastatic prostate cancer cells, after reaching the bone, adhere to and exit from marrow endothelium via transendothelial migration, undergo mesenchymal-to-epithelial transition (MET) and colonize in the bone by increased expression of cell–cell adhesive/junction proteins such as E-cadherin. The metastatic cascade is aided by the active participation of both resident fibroblasts, such as lymph node fibroblast (LNF), lung fibroblast (LF), and brain fibroblast (BF), and migrating stromal fibroblasts such as cells derived from mesenchymal stem cells (MHC) at primary and metastatic sites. The multipotent MHC can differentiate into inductive cell populations in the tumor microenvironment, including reactive stroma, macrophage, platelet, dendritic cell and T- and B-cells, in the primary and at metastatic sites, to 'mark' the site prior to the occurrence of secondary metastases

(Karnoub et al. 2007; Chung et al. 2006; Desgrosellier and Cheresh 2010; Ishikawa et al. 2008; Jung et al. 2009; Kaplan et al. 2005; Svineng et al. 2008). The therapeutic targeting of cancer cells, though necessary, is insufficient by itself to control the growth of localized and disseminated cancers. This has led to the acceptance of co-targeting both the cancer and its microenvironments, including stromal fibroblasts, the vascular endothelial network, immune cells and host humoral substances (Chung et al. 2005; Cress and Mohla 2004; Tu and Lin 2008; Vessella and Corey

2006; Pollard 2009). The unique cell signaling networks linking the behavior of cancer cells (i.e. cell proliferation, resistance to apoptosis, cell migration, invasion and metastasis) with the activation of key downstream signaling pathways can be exploited as new and promising druggable targets (Chung et al. 2006; Anastasiadis et al. 2003; Kang and Altieri 2009; Tasseff et al. 2010). In this review, we use prostate cancer as a model to dissect the critical determinants that regulate growth, differentiation and progression of prostate cancer to the skeleton, the lethal human prostate cancer phenotype.

Looking forward, the study of cancer-associated stromal fibroblasts is rapidly evolving and could take center stage in revealing the secrets of cancer cell evolution. Recent exciting discoveries include the reprogramming adult normal stromal fibroblasts to form induced pluripotent stem (iPS) cells capable of orchestrating the development and differentiation of an entire embryo (Takahashi and Yamanaka 2006; Yu et al. 2009; Okita et al. 2007; Park et al. 2008; Zhao et al. 2009b). These findings raise new questions about the pathways leading to stromal fibroblast heterogeneity and the potential of *in situ* reprogramming of adult stromal fibroblasts to undergo iPS transition in an organ-specific environment. iPS cells could serve as progenitor cells for a subsequent generation of derivative cells comprising the entire stromal microenvironments, raising the possibility of developing stroma-based cancer therapy in the future.

1.2 The Roles of Stromal Fibroblasts in the Context of Tumor Microenvironment

1.2.1 Local Microenvironment

Cancer growth and evolution is intimately controlled by its microenvironment, and cancer cells also contribute reciprocally to the active process of remodeling their microenvironment (Ingber 2008; Rhee et al. 2001; Pathak et al. 1997). Cancer cells secrete soluble factors such as EGF, IGFs, PDGF, VEGF, HGF, FGFs, and TGFβs which collectively stimulate pleiotropic signaling in converging multi-signaling pathways that induce activated stromal fibroblasts or myofibroblasts, with potent growth-promoting effect on cancer cells. Local microenvironments are heterogeneous and composed of resident vascular endothelial cells, smooth muscle cells, basal/stem cells and, to a lesser extent, cells from neural and neuroendocrine lineages that could interact with cancer cells in a reciprocal manner through secreted soluble factors and insoluble extracellular matrices. In addition to resident stromal fibroblasts, migrating mesenchymal stem cells from bone marrow, with either hematopoietic or mesenchymal lineage, also contribute to stromal heterogeneity. These cells, macrophages, platelets, dendritic cells, T- and B-cells, and activated stroma, are likely to support local cancer growth, progression and distant metastasis through complex cancer–stroma, cancer–immune and cancer–stem cell interactions

(Josson et al. 2010; Singh et al. 2009; Jaganathan et al. 2007; McKeithen et al. 2010). The local heterogeneity of stromal fibroblasts could be determined by their anatomical location. Our laboratory recently showed that human prostate stromal fibroblasts derived from the peripheral zone of the prostate gland are more inductive than stromal fibroblasts derived from the transitional or central zones, and these results are consistent with the observation that progressive prostate cancer is derived predominantly from the peripheral rather than transitional or central zones (Thalmann et al. 2009).

1.2.2 Distant Microenvironments

Because of the propensity of prostate cancer to metastasize to bone, which is considered lethal, much effort has focused on defining the bone microenvironment and the mechanisms of bone turnover, including enhanced bone resorption, that contribute to the ability of cancer cells to colonize bone. Several key cell types in the bone microenvironment are of particular importance. Among these are the osteoblasts (OBs), bone-forming cells derived from bone marrow mesenchymal stem cells (MSC). Upon interaction with soluble factors such as bone morphogenic proteins, TGFβs, EGF, FGFs, or PDGF, MSC can potentially differentiate into OBs, chondrocytes, or adipocytes. In addition, there are osteoclasts (OCs), bone resorbing cells derived from monocytes of hematopoietic mesenchymal cell lineage. OCs express receptor activator of NF-kappaB (RANK), a receptor responding to RANK ligand (RANKL), secreted by osteoblasts or prostate cancer cells, promoting maturation of OCs, inducing the fusion of monocytes to form activated multinucleated OCs. These matured multinucleated OCs contribute to bone resorption or bone turnover resulting in the release of soluble growth factors, nutrients, calcium ions, and extracellular matrices (Araujo and Logothetis 2009; Buckle et al. 2010; Mizutani et al. 2009). The actions of these soluble and matrix factors alter cancer cell adhesion, proliferation and survival and also the responsiveness of the host microenvironments toward factors secreted by both cancer cells and cells in cancer microenvironments. Collectively, the factors present in the cancer milieu could determine how cancer cell-induced osteoblastic or osteolytic lesions ultimately support cancer cell colonization in bone. In addition to the local action of cancer microenvironments, the factors secreted by cancer microenvironments could conceivably govern the propensity of secondary cancer metastases to organs such as the lung, liver, brain, and kidney.

1.3 The Plasticity of the Stromal Microenvironment

1.3.1 Reactive Stroma

In response to cancer growth, host stromal fibroblasts undergo a dramatic morphologic and/or biochemical transition to form “reactive stroma” in a desmoplas-

tic reaction much like the granulation tissues found at the site of wound healing (Tuxhorn et al. 2001, 2002; Malins et al. 2006). Although the desmoplastic reaction associated with human prostate cancer is less apparent than in human breast cancer and melanoma, the transition of stromal fibroblasts to myofibroblasts at the gene expression level is quite apparent. Upon transition to reactive stromal cells, they express more abundant and diverse classes of extracellular matrix proteins with altered expression of genes associated with myofibroblasts, such as α- and γ-smooth muscle actin, fibronectin, actin bundle, paladin, Thy1, and TGF-β1 (Sung et al. 2008; Untergasser et al. 2005; Dakhova et al. 2009). A number of soluble growth factors, when added directly to cultured stromal fibroblasts, have been shown to induce myofibroblast transition (Olaso et al. 2003; Cushing et al. 2008; Kennard et al. 2008; Kikuta et al. 2006). Direct interaction between reactive stroma and cancer cells has been observed to promote cancer growth. This is consistent with clinical observations where the detection of reactive stroma in the prostate cancer microenvironments, for example, predicts PSA recurrence and the clinical outcome in prostate cancer patients (Dakhova et al. 2009; Tothill et al. 2008; Yanagisawa et al. 2007). The engagement between cancer cells and reactive stroma could promote tissue reorganization involving the participation of the vascular network and migrating MSC and host stromal fibroblasts to lead to increased cancer growth (Zhao et al. 2009a; Santamaria-Martinez et al. 2009). The prevalence of myofibroblasts in the cancer environment has been shown in many different forms of cancer including colon, liver, lung, prostate, ovary, pancreas, and breast (Tuxhorn et al. 2001; Friedman et al. 1984; Garin-Chesa et al. 1990; Radisky and Przybylo 2008; Yao et al. 2009). The myofibroblastic appearance often precedes the onset of cancer invasion.

1.3.2 Plasticity of EMT and MET

Dynamic bi-directional epithelial-to-mesenchyme (EMT) and mesenchymal-to-epithelial (MET) transitions have been observed in embryonic development and in cancer progression (Chung et al. 2006; Prindull 2005; Birchmeier et al. 1996; Wells et al. 2008; Hugo et al. 2007). These transitions are commonly associated with a predictive switch of cancer behaviors by the affected cancer epithelium, which assumes increased migratory, invasive and metastatic potential, as assessed by changes in cell morphology and gene expression profiles. This is the rationale for designing novel EMT/MET-based targeting strategies (Sabbah et al. 2008; Moen et al. 2009; Ponzo et al. 2009). In the context of cancer microenvironments, these transitions offer a possible new explanation of the origins of the inductive stromal fibroblasts and the responding cancer epithelial cells, since both cancer epithelial cells and stromal fibroblasts can be derived from either resident or migrating pluripotent stem cells or from a selective population of transforming cancer epithelial or reactive stromal cells through interactions with specific cell types or factors in the cancer microenvironment (Santamaria-Martinez et al. 2009; Leber and Efferth 2009). A small side population of pancreatic cancer stem cells was recently reported to be particularly sensitive to EMT induction by TGF-β (Kabashima et al. 2009).

Likewise, circulating cancer cells were shown to be sensitive to growth factor induction to undergo EMT and MET (Vessella et al. personal communication).

1.3.3 Mesenchymal Stem Cells (MSC)

MSC are a class of multipotent stem cells capable of differentiating into osteoblasts, chondrocytes, and adipocytes. They can be derived from bone marrow stromal cells and also from adult linage stem cells with self-renewal capability. These cells were found to be present in cancer microenvironments, with the potential of promoting cancer growth and progression (Roorda et al. 2009), exerting immunosuppression by interfering with dendritic and T-cell functions (Spaeth et al. 2008) and 'marking' the sites where cancer cells subsequently metastasize (Jung et al. 2009; Kaplan et al. 2005). These functions are generally accomplished by the ability of MSC to secrete specific factors which, via circulatory network and paracrine interaction, confer migratory, invasive and metastatic potential to cancer cells at the primary site of cancer growth. They also interact at the site of metastasis, for instance by increasing bone turnover to create a favorable microenvironment supporting the dissemination of cancer cells (Kaplan et al. 2007).

1.4 The Mediators and Cell Signaling Network Governing the Plasticity of Stromal Fibroblasts

Soluble and insoluble mediators secreted by cancer cells and cells in cancer microenvironments are responsible for supporting the growth and progression of cancer by interacting with selective receptors that transmit signals orchestrating a switch in cancer cell morphology and function compatible with the survival of cancer cells. In this section, specific examples defining prostate cancer interactions with soluble and matrix proteins will be used to illustrate the importance of understanding the cell signaling network to identify relevant therapeutic targets for clinical translation and develop new drugs.

1.4.1 Soluble Growth Factors

The general model depicted in Fig. 1.1 shows cancer cell-secreted soluble factors promoting the activation of both cancer-associated resident stromal fibroblasts and migrating MSC and/or their derivative stromal fibroblasts. This triggers additional remodeling of tumor microenvironments, reciprocally affecting the genotype and phenotype of both cancer cells and stromal fibroblasts in the cancer microenvironment via soluble factors including growth factors, cytokines, chemokines, and

reactive oxygen species (ROS) released in the tumor microenvironment by resident and migrating host mesenchymal or stromal cells. These factors often work in concert to induce a primarily stromal reaction manifested by activated stromal fibroblasts or myofibroblasts producing either higher levels and/or more effective combinations of soluble growth factors capable of inducing cancer growth, invasion and metastasis directly, and also of promoting the reorganization of the vascular network favoring the dissemination of cancer cells to distant organs. In other words, soluble factors produced by cancer and host stroma can be disseminated to distant sites where they become responsible for remodeling the premetastatic niche and facilitating subsequent cancer cell dissemination (Kaplan et al. 2007). In some cases, soluble factors can act at long distance at metastatic sites to modulate tumor microenvironments by providing higher concentrations or more complementary growth factors via increased bone turnover, creating a less hostile environment for the growth of cancer cells via immune suppression, or promoting osteomimicry within cancer cells and creating a metastatic bone 'niche' favoring overall cancer cell growth and survival at metastatic sites (Chung et al. 2006; Cooper et al. 2003). Soluble factors secreted by cancer and activated stromal cell components within the tumor microenvironment can also modulate other cell signaling networks mediated by integrin-extracellular matrix interactions (Sangaletti et al. 2008; Chiarugi and Giannoni 2005) and androgen receptor signaling pathways (Huang et al. 2006; Olapade-Olaopa et al. 1999), activating the cell signaling network to upregulate integrins and/or androgen receptor expression (Liegibel et al. 2002; Bonaccorsi et al. 2006).

1.4.2 Extracellular Matrices (ECMs)

Cancer cell proliferation and survival within the tumor microenvironment depends on the ability to adhere and attach to ECMs (Desgrosellier and Cheresh 2010). Through ECM-integrin interactions, cancer cells can also gain increased invasive, migratory and metastatic potential, mediated by the activation of converging cell signaling networks downstream that confer growth and survival advantages to cancer cells (Pontier and Muller 2009). ECM-integrin interactions, known to affect embryonic development (Armant 2005), also play a directive role in determining the gene expression profiles of cancer cells, the ability of cancer cells to degrade their surrounding ECMs by matrix metalloproteinases (MMPs), to extravasate into metastatic microenvironments by adhesion to organ-specific endothelial cells (Kargozaran et al. 2007), and the status of differentiation of cancer cells.

1.4.3 ROS and Oxidative Stress

High levels of ROS and oxidative stress can be created in cancer microenvironments by the continued growth and expansion of solid tumors which deplete oxygen

supplies and build up metabolic waste at the site of tumor growth. Cancer cells with downregulated manganese superoxide dismutase (MnSOD) show increased levels of superoxide, which induce hypoxia inducing factor 1 (HIF-1α) and VEGF, causing increased angiogenesis and tumor growth (Kaewpila et al. 2008; Wang et al. 2005). An accumulation of hydrogen peroxide can also be induced by placing cancer cells under hypoxic conditions and in cells with defective catalase (Azad et al. 2009). Hydrogen peroxide is a potential mediator contributing to the co-evolution of the genotype and phenotype of both prostate cancer and bone stroma when they are in contact under 3-D co-culture conditions (Sung et al. 2006, 2008). Hypoxic conditions can also affect the transdifferentiation of cancer cells such as EMT and MET, where hypoxia induces EMT (Klymkowsky and Savagner 2009; Jiang et al. 2007) and hyperbaric oxygen treatment causes MET (Moen et al. 2009) with respective corresponding changes of either increased or decreased cancer growth and invasion in animals.

1.5 Overall Significance and Clinical Translation of Integrated Approaches to Cancer–Stromal Fibroblast Interaction

Our laboratory has established a 3-dimensional (3-D) co-culture system to investigate how the information derived from cancer–stromal fibroblast interaction can be applied in the clinic and to understand the molecular pathways that determine the behaviors of cancer cells. This approach is based on our prior work showing that cancer cell phenotype and genotype can be irreversibly "programmed" when cancer cells are grown together with prostate or bone stromal cells under 3-D conditions as prostate organoids (Sung et al. 2008; Rhee et al. 2001) or in mice as tumor xenografts (Sung et al. 2008). We found several important features of these types of cellular interactions. (1) The irreversible "programming" of the phenotype and genotype of cancer cells by stromal fibroblasts is bi-directional. We observed that human stromal fibroblasts co-cultured with human prostate cancer cells under 3-D conditions can program the genotype (assessed by cytogenetics and genome-wide scan (Sung et al. 2008) and phenotype (measured by gene expression and ability to grow tumors with metastatic potential in mice (Sung et al. 2008). Remarkably, normal stromal fibroblasts from mouse, benign/normal human prostate stromal fibroblasts, and the MG-63 osteosarcoma cell line have also been observed to undergo irreversible and non-random genotypic and phenotypic changes when co-cultured with prostate cancer cells under 3-D conditions (Sung et al. 2008; Rhee et al. 2001). (2) Gene expression analyses revealed that stromal fibroblasts, after physical contact with prostate cancer cells, had increased levels of brain-derived neurotropic factor (BDNF), chemokines, CCL5 and CXCL5, versican, tenascin, connective tissue growth factor, stromal cell derived factor-1 (SDF-1/CXCL12), and HIF-1α (Sung et al. 2008). We have validated the overexpression of these biomarkers identified by our cell culture model in clinical tissue and serum samples collected from

prostate cancer patients with confirmed bone metastasis (Sung et al. 2008). These studies highlight the bidirectional interactions and the co-evolution of tumor-stroma in prostate cancer progression.

1.6 Co-targeting Tumor and Stroma as an Effective Therapeutic Strategy for the Treatment of Cancer and Cancer Metastasis

Cancer-host microenvironment communication in the primary and at distant metastatic sites, mediated by soluble factors and insoluble matrices, supports the growth and survival of cancer cells. This provides a sound rationale for co-targeting both the tumor and the host microenvironment to achieve better tumor growth control and improve overall patient survival. Cancer development is complex, involving multiple interactions between different cell types and pleiotropic signaling mechanisms leading to progression. Reciprocal interaction between prostate cancer cells and resident and migrating cells in the tumor microenvironments mediated by cell signaling networks should be considered viable targets. Prostate cancer frequently metastasizes to bone and <50% of the patients with hormonal refractory bone metastases survive more than 5 years. Our laboratory has addressed the critical issues of prostate cancer bone metastasis from both the biological and therapeutic perspectives (Chung et al. 2006; Josson et al. 2010; Chung 1993, 1995). We investigated human prostate cancer cell interaction with human osteoclasts, osteoblasts and marrow stromal cells under 3-D co-culture conditions to mimic tumor growth *in vivo* (Sung et al. 2008). These studies allowed us to conclude that prostate cancer survives in a tumor microenvironment by the activation of specific cell signaling networks with neighboring host cells. During this process, the cancer cells and cells in the cancer microenvironment "co-evolve" in part through their response to growth factors, extra-cellular matrices and ROS (Sung et al. 2008; Rhee et al. 2001; Thalmann et al. 1994). Cancer cells acquire several mimetic abilities, such as osteomimicry, vasculomimicry, neuromimicry and stem cell mimicry, and undergo a transition from epithelium to mesenchyme with definitive behavioral modifications (Huang et al. 2006; Zhau et al. 2008). To develop an effective targeting strategy for prostate cancer bone metastases, it is critical to consider these interactions and devise the most effective way of *targeting not only tumor cells, but also cells in the tumor microenvironment* (Hsieh et al. 2004; Kubo et al. 2003).

Table 1.1 summarizes a number of ongoing and completed clinical trials proving the concept that the tumor-associated stroma compartment is a new and exciting target awaiting the development of novel therapeutics. Our laboratory first conducted a clinical trial co-targeting prostate cancer and bone with an adenoviral-based therapy using a therapeutic toxic gene driven by an osteocalcin promoter shared in common by cancer and bone cells (Hsieh et al. 2004; Kubo et al. 2003). A number of successful avenues have been opened, including co-targeting the interaction of prostate cancer and endothelium via VEGF-mediated signaling with an antibody (e.g.

Table 1.1 Soluble growth factors and cells in the bone become attractive targets for the development of novel biological-based therapeutics for the management of prostate cancer local growth and distant metastases to bone and soft tissues

Therapeutic targets (growth factors, cells)	Drugs	References
Human epidermal growth factor (hEGF)	Trastuzumab (Herceptin®), Lapatinib (Tykerb®), Gefitinib (Iressa®), Erlotinib (Tarceva®), Cetuximab (Erbitux®), Panitumumab (Vectibix®)	http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted
Vascular endothelial growth factor (VEGF)	Bevacizumab (Avastin®), Ranibizumab (Lucentis), Lapatinib (Tykerb), Sunitinib (Sutent), Sorafenib (Nexavar), Axitinib, Pazopanib	http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted, http://en.wikipedia.org/wiki/Vascular_endothelial_growth_factor
Transforming growth factor-beta (TGF-β)	AP12009 (Trabedersen), antisense oligonucleotide against TGF-β2 (Phase III), GC1008 anti-TGF-β monoclonal antibody (Phase I)	Garber (2009)
Insulin growth factor-1 receptor (IGF1R)	CP-751,871 (monoclonal antibody) Phase I, AP-12 (monoclonal antibody) Preclinical, 19D12 (monoclonal antibody) Preclinical, EM164 (monoclonal antibody) Preclinical, hC7C10 (monoclonal antibody) Preclinical	Garber (2005)
Platelet derived growth factor (PDGFR)	SU-101 kinase inhibitor, Phase III, Gleevec	Gibbs (2000)
Endothelin receptor	Atrasentan	Lalich et al. (2007)
Radiolabelled antibodies—Prostate specific membrane antigen (PSMA)	^{177}Lu-labelled J591, ^{90}Y-labelled J591	Bander et al. (2005); Milowsky et al. (2004)
Radiolabelled antibodies—Prostate stem cell antigen (PSCA)	AGS-PSCA (Phase I)	David et al. (2006)
Integrins	Monoclonal antibodies targeting the extracellular domain of the heterodimer: Vitaxin Synthetic peptides containing an RGD sequence: Cilengitide; KGaA Peptidomimetics of RGD sequence: S247	Stupp et al. (2007)
Integrins-αv family	CNTO 095	Trikha et al. (2004)
Osteoclasts	Bisphosphonates: Non-N-containing bisphosphonates:Etidronate (Didronel), Clodronate (Bonefos, Loron) Tiludronate (Skelid)N-containing bisphosphonates: Pamidronate (APD, Aredia), Neridronate, Olpadronate, Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel), Zoledronate (Zometa, Aclasta)	http://en.wikipedia.org/wiki/Bisphosphonate

Table 1.1 (continued)

Therapeutic targets (growth factors, cells)	Drugs	References
Osteoclasts	Bone-seeking radiopharmaceuticals: Radium-223 (Alpharadin®), strontium-89, samarium-153	Nilsson et al. (2007); Tu et al. (2005)
Osteoclasts (RANKL)	Denosumab (Prolia)	http://en.wikipedia.org/wiki/Denosumab

bevacizumab) or small molecules to inhibit receptor tyrosine kinases (e.g. sunitinib); co-targeting interactions between prostate cancer and a number of soluble growth factors secreted by cancer, stromal fibroblasts and/or inflammatory cells using either therapeutic antibodies (Chung et al. 2005; Wu et al. 2005) or small molecule tyrosine kinase inhibitors; and co-targeting the prostate cancer/osteoblast interface with the endothelin receptor antagonists Zibotentan or Atrasentan (Kopetz et al. 2002). Co-targeting extracellular matrix-prostate cancer interactions with integrin antagonists against αvβ3 (e.g. Vitaxin) or αv (e.g. CNTO95) has been tested. Bone-directed co-targeting with a RANKL antibody, denosumab, or osteoclast antagonists, bisphosphonates, has helped to reduce bone pain and skeletal-related events (SRE) (Keller 2002; Saad et al. 2009). Co-targeting patients with confirmed bone metastases with radiopharmaceutics, ^{89}Sr, ^{153}Sm (β-emitters), or ^{188}Re (γ-emitter) radionuclides, plus chemotherapy (e.g. docetaxel, mitoxantrone, estramustine and etoposide), long-term androgen suppression and/or external beam radiation has also improved quality of life and prostate cancer patient survival (Sartor 2009; Tu et al. 2005).

A common drawback in these trials is the severe marrow toxicity encountered by patients treated with the co-targeting agents. So far, this has compromised the prospect of repeated administration of these highly effective agents to prostate cancer patients for potential "cure". Recently, an exciting therapeutic development using bone-seeking ^{223}Ra, an α-emitter, for the treatment of prostate cancer bone metastases has been explored (Nilsson et al. 2005, 2007). ^{223}Ra has the advantage of emitting high linear energy transfer (LET) radiation with a short track length in tissues for up to just a few mm. In a randomized, multicentre placebo-controlled phase II trial (Nilsson et al. 2005, 2007), ^{223}Ra was found to be well-tolerated, sparing myelotoxicity while reducing serum bone-alkaline phosphatase concentration, a marker indicative of prostate cancer growth in bone in patients with bone metastases. ^{223}Ra prevented SRE and improved overall survival in patients with hormone-refractory prostate cancer. ^{223}Ra is currently in Phase III trials in the US and Europe in patients with metastatic prostate cancer bone metastases.

1.7 The Frontier of Future Stromal Fibroblast Research

The plasticity of stromal fibroblasts and their ability to induce cancer cell growth, migration, invasion and metastasis, to promote cancer cell survival, and to alter cancer cell sensitivity toward chemotherapy and radiation therapy raises the fol-

lowing questions, which can be considered as some of the future frontiers of stromal fibroblastic research. (1) What are the regulatory mechanisms determining the plasticity and differentiation status of stromal fibroblasts? The intriguing biology of iPS cells taught us the lesson that a normal adult stromal fibroblast can be reprogrammed by the introduction of a cassette of transcription factors, *Oct4, Sox2. Klf4 and c-Myc,* to become pluripotent stem cells capable of forming cells and organs of diverse lineages including inductive stromal fibroblasts and MSCs. The critical question that needs to be addressed is whether the engineered transcription factor protein(s) produced within tumor microenvironments can play the reprogramming roles of an adult stromal fibroblast and explain the heterogeneity of stromal fibroblasts. This speculation has now been supported by a stunning laboratory demonstration where recombinant transcription factor proteins, when added to cultured adult stromal fibroblasts, reprogrammed these cells to express markers indicative of a stem cells phenotype (Cho et al. 2010; Tang et al. 2010; Rhee et al. 2011). This suggests the possibility that proteins secreted by cancer cells and cells in the tumor microenvironments could reprogram adult cells and that this could be the molecular basis of the reactivation of embryonic growth potential of the stroma, proposed more than three decades ago by McNeil as a contributing factor to benign hyperplastic growth of the prostate gland (BPH) commonly found in the aging male (McNeal 1978). (2) What are the critical soluble factors and ECMs produced by cells in tumor microenvironments that can dictate the growth, survival and metastasis of malignant prostate cancer cells? Published data suggest that a host of factors, including classical soluble growth and survival factors, ROS, chemokines and cytokines, ECMs and their fragments, can modulate cancer–cancer and cancer–stroma interactions. It is becoming increasingly important to reclassify these factors and their combinations based on their molecular actions with special emphasis on factors that confer *lethal* phenotypes to cancer cells. Developing better tools to predict the clinical outcome of prostate cancer will support the concept and its implementation in personalized and predictive oncology for improved diagnosis, prognosis and treatment of patients with prostate cancer. (3) What are the most effective means of co-targeting tumor and stroma to prevent cancer cells from developing therapeutic resistance? There are an increasing number of clinical trials based on the concept of co-targeting cancer and cancer-associated microenvironments. An improved fundamental understanding of how tumor–stroma interacts, and how the genotype and phenotype of cancer cells may be "co-evoluted" will help us developing better and more effective co-targeting strategies for the management of lethal prostate cancer.

Acknowledgements The author wishes to thank Dr. Sajni Josson for her help in the construction of the figure and the table. The editorial assistance from Gary Mawyer is also appreciated. This work was supported in part by the following grants: R01 CA122602 and P01 CA098912 from National Caner Institute and W81 XWH-01–1-0172 from Department of Defense, United States Army.

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