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Targeting breast cancer through its microenvironment: Current status of preclinical and clinical research in finding relevant targets

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ABSTRACT

It is increasingly evident that not only breast cancer cells, but also the tissue embedding these cells: the tumor microenvironment, plays an important role in tumor progression, metastasis formation and treatment sensitivity. This review focuses on the current knowledge of processes by which the microenvironment affects breast cancer, including formation of the metastatic niche, metabolic stimulation, stimulation of tumor cell migration, immune modulation, angiogenesis and matrix remodeling. The number of drugs targeting key factors in these processes is expanding, and the available clinical data is increasing. Therefore current strategies for intervention and prediction of treatment response are outlined. At present, targeting the formation of the metastatic niche and metabolic stimulation by the breast cancer microenvironment, are already showing clinical efficacy. Intervening in the stimulation of tumor cell migration and immune modulation by the microenvironment upcoming fields of great research interest. In contrast, targeting microenvironmental angiogenesis or matrix remodeling appears to be of limited clinical relevance in breast cancer treatment so far. Further research is warranted to optimize intervention strategies and develop predictive tests for the relevance of targeting involved factors within the microenvironment in order to optimally personalize breast cancer treatment.

Contents

Abbreviations: ^{18}F, Fluor-18; ^{89}Zr, zirconium-89; ^{111}In, indium; CAF, cancer associated fibroblast; cMET, C-mesenchymal–epithelial transition factor; CSF, colony stimulating factor; CI, confidence interval; CTLA, cytotoxic T lymphocyte-associated antigen; CXCL, chemokine (C-X-C motif) ligand; CXCR, C-X-C motif receptor; E2, estradiol; ECM, extracellular matrix; ER, estrogen receptor; FES, fluoroestradiol; HER, human epidermal growth factor receptor; HGF, hepatocyte growth factor; HR, hazard ratio; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor 1 receptor; IL, interleukin; IR, insulin receptor; LOX, lysyl oxidase; LOXL, lysyl oxidase ligand; MAPK, mitogen-activated protein kinase; MBC, metastatic breast cancer; MDSC, myeloid-derived suppressor cells; MMP, matrix metalloprotease; OPG, osteoprotegerin; PD, programmed cell death; PD-L, programmed cell death ligand; PET, positron emission tomography; PI3K, phosphoinositide 3-kinase; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor κB; RANKL, receptor activator of nuclear factor κ ligand; SDF, stromal derived growth factor; SUV, standardized uptake value; TAM, tumor-associated macrophage; TGFβ, transforming growth factor β; TGFβR, transforming growth factor β receptor; TIL, tumor infiltrating lymphocyte; TKI, tyrosine kinase inhibitor; TNBC, triple negative breast cancer; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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1. Introduction

Breast cancer is the most common cause of cancer death among women worldwide (Ferlay et al., 2010). In 2010, 207,090 women were diagnosed with breast cancer in the United States (Jemal et al., 2010). ~6% of all breast cancer patients have metastatic disease at the time of diagnosis, and currently 20% will eventually develop metastatic breast cancer (MBC) (Howlader et al., 2012). Once metastasized, breast cancer is generally incurable.

Recent treatment strategies focus on induction of tumor cell death using chemotherapeutic, anti-hormonal and targeted agents. However, it is increasingly recognized that not only the tumor cells, but also the tissue embedding the tumor cells; their microenvironment, plays an important role in tumor progression and metastasis. This role in the complexity of metastasis (Fidler, 2003) can be assumed from the metastatic pattern of breast cancer to specific organs (Kennecke et al., 2010). The importance of the cancer microenvironment is underlined by the recent inclusion of the microenvironment in the so called "hallmarks of cancer" (Hanahan & Weinberg, 2011; Hanahan & Coussens, 2012). Furthermore, microenvironmental characteristics affect breast cancer prognosis and chemosensitivity, and as such are increasingly incorporated in gene expression profiles (Fumagalli & Sotiriou, 2010; Morales et al., 2011). Novel drugs targeting key factors in the microenvironment are being developed.

The tumor microenvironment includes soluble factors, extracellular matrix (ECM) and stromal cells (Egeblad et al., 2010). Involved soluble factors comprise growth factors, hormones, immunoglobulins, cytokines and chemokines (Egeblad et al., 2010). The ECM contains proteoglycans, hyaluronic acid and fibrous proteins (collagen, fibronectin and laminin). Involved stromal cells include fibroblasts, (pre-)adipocytes, cells of the vascular system (endothelial cells) and immune cells (Wiseman, 2002; Polyak & Kalluri, 2010). Combinations of different cellular, extracellular and soluble factors can act to support multiple processes in the breast cancer microenvironment that promote progression and metastasis. This review focuses on the current knowledge of processes involved in the breast cancer microenvironment, and how they affect breast cancer progression and metastasis. These processes include: formation of the metastatic niche, metabolic stimulation, stimulation of tumor cell migration, immune modulation, angiogenesis and matrix remodeling. We will place them in the current order of importance as targets for breast cancer therapy, based on the clinical evidence with the available targeting agents (Table 1). Per factor involved in the processes, the mechanism of action and preclinical data is described, which is followed by the currently available clinical data. Thereafter, the present data regarding treatment response prediction is outlined per factor. Finally, we will describe potential future directions exploiting the microenvironment in breast cancer treatment.

2. Search strategies and selection criteria

Articles for this review were found by searches from PubMed, abstracts from the American Association for Cancer Research (AACR) and American Society of Clinical Oncology (ASCO) and the clinicaltrials.gov database by use of the terms 'breast cancer', 'microenvironment' combined with 'metastasis' 'metabolic dysfunction' 'migration' 'immune cells' 'angiogenesis' or 'matrix remodeling' and combinations of these terms with the selected soluble factors. In addition, relevant papers from the reference lists of selected papers were included. Only studies written in English were included.

3. Formation of the metastatic niche

The importance of the interaction of the breast cancer cells with their microenvironment has long been suggested by the specificity of the metastatic pattern (Paget, 1889). In MBC patients, metastasis patterns even differ per breast cancer subtype (Kennecke et al., 2010). In general however, bone is by far the most common metastatic site involving 65% of patients with MBC (Chaudary, 1991; Jain et al., 1993; Kennecke et al., 2010). Crucial factors involved in the development of bone metastases are transforming growth factor (TGF)β and receptor activator of nuclear factor κB ligand (RANKL) (Fig. 1A).

3.1. TGFβ — mechanism of action and preclinical data

The cytokine TGFβ has tumor suppressive properties in the physiological setting. However, during malignant progression, TGFβ signaling promotes growth, progression and invasion of the tumor (Massagué, 2008). Both cancer and cancer associated fibroblasts (CAF)s excrete TGFβ by autocrine as well as paracrine secretion, giving rise to a tumor-promoting microenvironment (Kojima et al., 2010; Guido et al., 2012) (Fig. 1A.1 (circle tumor cell) and A.2 (circle microenvironment)). Activated TGFβ binds to the TGFβI- and TGFβII-receptor (−R) which both induce Smad2 phosphorylation which in turn activates transcriptional factors (Padua & Massague, 2009). In human triple negative breast cancer (TNBC) metastatic models in mice, reducing TGFβ signaling, either pharmacologically (with pan-TGFβ antibody 1D11 or TGFβ receptor inhibitor Ki26894 or LY2109761 or molecularly (with a short hairpin against Smad4), reduced metastases (Ehata et al., 2007; Korpal et al., 2009; Ganapathy et al., 2010) (Fig. 1A.3 (circle targeting)). However, in a metastatic human luminal breast cancer mouse model, targeting TGFβ signaling with 1D11 did not influence metastasis formation after intracardiac breast cancer cell injection (Ganapathy et al., 2012). Moreover, deletion of the TgfβII receptor gene in mouse mammary epithelial cells increased tumor growth and pulmonary metastasis formation (Bierie et al., 2008). This suggests not only that targeting of TGFβ in early phases of tumorigenesis has tumor promoting effects, but also that there is likely to be a breast cancer subtype specific aspect to this.

TGFβ is also described to be implicated in epithelial mesenchymal transition (EMT). This change in phenotype allows cancer cells to increase metastatic potential (Scheel et al., 2011). Although debate about the clinical relevance and existence of EMT still exists (Ledford, 2011; Roxanis, 2013), preclinical evidence for a role of TGFβ in breast cancer EMT is present. TGFβ derived from CAFs, isolated from human breast cancer tissue, was shown to induce an EMT like phenotype of breast cancer cells MCF-7, MDA-MB-231 and T47D in vitro, characterized by increased vimentin, fibronectin, matrix metalloprotease (MMP) expression and increased migration (Yu et al., 2014). This phenotype was inhibited by adding a TGFβ neutralizing antibody. In a rat mammary cancer model MTLn3E, (transient) TGFβ signaling was active in single cell motility of breast cancer cells, which led to hematogenous spread and pulmonary metastases. Blocking TGFβ signaling genetically reduced hematogenous spread but did not affect local metastasis to lymph nodes (Giampieri et al., 2009). These data indicate that TGFβ signaling can phenotypically change breast cancer cells, inducing metastatic characteristics.

TGFβ signaling can be inhibited by bisphosphonates(Fig. 1A.3). Bisphosphonates are commonly used as supportive treatment in MBC patients with bone metastases. In a metastatic mouse model with