Molecular and Cellular Endocrinology 382 (2014) 673–682

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

The immune system and inflammation in breast cancer

Xinguo Jiang [a,*], David J. Shapiro [b,*]

[a] Department of Medicine, VA Palo Alto Health Care System/Stanford University School of Medicine, Stanford, CA 94305, USA
[b] Department of Biochemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

ARTICLE INFO

Article history:
Available online 19 June 2013

Keywords:
Breast cancer
Immunity
Inflammation
Immunosurveillance
ER-alpha

ABSTRACT

During different stages of tumor development the immune system can either identify and destroy tumors, or promote their growth. Therapies targeting the immune system have emerged as a promising treatment modality for breast cancer, and immunotherapeutic strategies are being examined in preclinical and clinical models. However, our understanding of the complex interplay between cells of the immune system and breast cancer cells is incomplete. In this article, we review recent findings showing how the immune system plays dual host-protective and tumor-promoting roles in breast cancer initiation and progression. We then discuss estrogen receptor α (ERα)-dependent and ERα-independent mechanisms that shield breast cancers from immunosurveillance and enable breast cancer cells to evade immune cell induced apoptosis and produce an immunosuppressive tumor microenvironment. Finally, we discuss protumorigenic inflammation that is induced during tumor progression and therapy, and how inflammation promotes more aggressive phenotypes in ERα positive breast cancers.

1. Introduction

Despite significant therapeutic achievements in recent years, in industrialized countries, breast cancer remains the most common cancer in women. It causes about 40,000 deaths in the United States each year (Basu et al., 2012). Estrogen receptorα (ERα) positive breast cancers represent more than 70% of breast tumors and endocrine therapies such as selective estrogen receptor modulators (SERMs) and aromatase inhibitors are still the standard adjuvant treatment for these tumors. However, the majority of patients will develop resistance to hormonal therapy and will need alternative therapies (Clarke et al., 2001; Clarke et al., 2003; Osborne and Schiff, 2011).

For over a century, the idea that the immune system can control cancer has been a subject of debate. Only very recently has it become generally accepted that the immune system has the ability not only to prevent tumor growth but also to promote it through a process called immunoediting. This process is comprised of three phases: elimination, equilibrium and escape (Schreiber et al., 2011; Vesely et al., 2011). Elimination is achieved through identification and destruction of nascent transformed cells by acute tumor-inhibiting inflammation, characterized by infiltration of effector cells of the innate and adaptive immune system as well as production of tumor-inhibiting cytokines. The escape phase is sustained by chronic tumor-promoting inflammation, which mainly involves immunosuppressive cells and soluble factors (Vesely et al., 2011). Evading immune destruction has recently been recognized as a hallmark of cancer (Hanahan and Weinberg, 2011). In general, use of immunosuppressants following organ transplantation or HIV infection increases the risk of tumors such as skin cancer, non-Hodgkin's lymphoma or lung cancers, but not cancers of organs such as breast, brain, prostate and ovary (Kirk et al., 2007; Jiang et al., 2010). These studies suggest that breast cancer cells may be less immunogenic or simply take longer to develop (Vesely et al., 2011). Historically pre-existing inflammation or infection was not considered to be an underlying risk factor for the development of breast cancer. However, it is now clear that the infiltration of leukocytes, in the correct context, can either eliminate or promote the development of breast cancers (DeNardo and Coussens, 2007; Coussens and Pollard, 2011). Several studies have shown that immunity and inflammation-associated gene expression signatures are able to predict or classify tamoxifen-resistant breast cancers (Jansen et al., 2005; Chanrion et al., 2008; Vendrell et al., 2008). This supports the notion that endocrine resistance is associated with a dysregulated immune response and/or excessive inflammation in the tumor microenvironment (Osborne and Schiff, 2011). A recent study suggests that the immune response profile and inflammatory signature in breast cancer may provide useful information on patient prognosis and treatment (Kristensen et al., 2012). These studies suggest that research associated with

* Corresponding authors. Addresses: VA Palo Alto Health Care System, 3801 Miranda Avenue, Bldg 101, A4-151 Palo Alto, CA 94304, USA. Tel.: +1 (650) 493 5000x64771 (X. Jiang), 314D Roger Adams Lab, 600 S. Mathews Avenue, Urbana, IL 61801, USA. Tel.: +1 (217) 333 1788; fax: +1 (217) 244 5858 (D. Shapiro).
E-mail addresses: xinguoj@stanford.edu (X. Jiang), djshapir@life.illinois.edu (D.J. Shapiro).

0303-7207/$ - see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.mce.2013.06.003

inflammation and the immune system may enhance therapeutic possibilities for breast cancers, especially for those resistant to endocrine therapies. To better understand the battle and interplay between breast cancer cells and cells of the immune system, in this review we discuss following topics: (1) anti-breast cancer effector cells of the immune system, (2) mechanisms of breast cancer resistance to antitumor immunity, (3) protumorigenic inflammation in breast cancer and (4) inflammation promotion of aggressive phenotypes of ERα positive breast cancer.

2. Anti-breast cancer effector cells of the immune system

Breast cancer is often initiated by genetic and epigenetic changes in genes that regulate the function of the mammary epithelial cells (Coussens and Pollard, 2011). To prevent the development of breast cancer, diverse intrinsic tumor-suppressor mechanisms induce senescence or apoptosis of neoplastic cells (Lacroix et al., 2006; Xu et al., 2011; Nicholls et al., 2012). In parallel, the immune system is recognized as an extrinsic tumor-suppressor that can eliminate epithelial cells that have transformed to breast cancer cells and limit their growth when they have escaped intrinsic tumor suppression mechanisms (Schreiber et al., 2011; Vesely et al., 2011). The contribution of the immune system to breast cancer progression and inhibition is summarized in Fig. 1.

2.1. Cytotoxic T lymphocytes (CTLs) as anti-breast cancer effector cells

The primary effector immune cells that eliminate breast cancer cells are CD8+ CTLs and natural killer (NK) cells. Numerous studies have revealed that CTLs can be induced to target specific antigens expressed on breast cancer cells (Disis et al., 1994; Peoples et al., 1995; Kontani et al., 2001; Neidhardt-Berard et al., 2004; Treilleux et al., 2004; Wang et al., 2006; Mine et al., 2009; Mittendorf et al., 2012). CD8+ T lymphocyte infiltration is associated with better overall patient outcomes, independent of other prognostic factors such as tumor grade, lymph node stage, size, vascular invasion and HER2 status. Morever, CD8+ T cell infiltration is associated with better breast cancer-specific survival in subgroups of patients with ERα-negative, HER2-negative or basal phenotype (Mahmoud et al., 2011). Consistent with this finding, another study showed that CD8+ T cell infiltration was associated with better patient survival in basal-like but not in non-basal triple negative breast cancers; on the contrary, CD8+ T cell infiltration was not prognostic in ER^+ populations. These observations may suggest that the ER^+ subgroup of breast cancer is less immunogenic than other subtypes (Liu et al., 2012). Combined chemotherapy with immunotherapy increases cytolytic activity of CTLs, which results in substantial enhancement of the antitumor effect (Ramakrishnan et al., 2010). The effect of vaccines against breast cancers is at least partly achieved through enhanced recognition and destruction of breast cancer cells by CTLs (Rech et al., 2012, Schlom, 2012, Wang et al., 2012). Together, these studies strongly suggest that CD8+ T cells have clinically significant antitumor activity against human breast cancer, and that the prognostic role of tumor infiltrated CTLs is dependent on the breast cancer subtype.

2.2. NK cells as anti-breast cancer effector cells

NK cells are cells of the innate immune system that kill tumor cells without MHC restriction (Waldhauer and Steinle, 2008). Decreased NK cell activity has been reported in patients with familial breast cancer as well as in their clinically asymptomatic first degree relatives (Strayer et al., 1986). NK cell activity was significantly reduced in different stages of breast cancers, with stage IV tumors showing reduced NK cell activity compared with stage I–III tumors (Konjevic and Spuzic, 1993). NK cell dysfunction is associated with human breast cancer progression (Mamessier et al., 2011). Unsupervised gene expression profiling of breast cancer-associated stroma revealed a gene signature that was functionally enriched in the expression of genes associated with CTLs and NK cells and was predictive of better clinical outcomes (Finak et al., 2008). Immunization against Stat3 in a mouse breast cancer xenograft model elicits strong antitumor immunity through memory CD4+ T cell dependent NK cell mediated cytotoxicity (Tkach et al., 2012). IL-2 or IL-15-activated NK cells potentiate the activity of cetuximab against triple negative breast cancer (Roberti et al.,

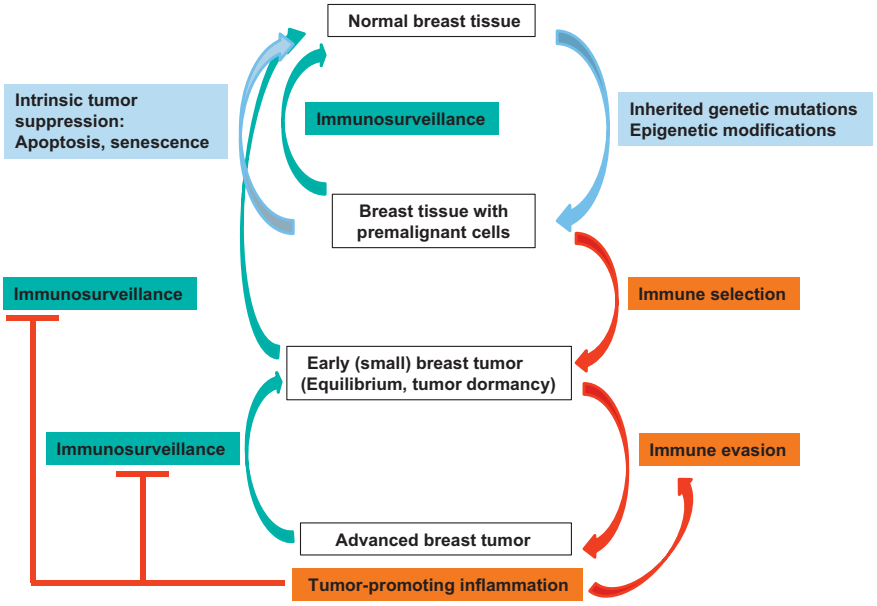

Fig. 1. Immunosurveillance and inflammation in breast cancer. Inherited genetic mutation and epigenetic modifications cause premalignant transformation of mammary cells. Transformed cells can be eliminated by intrinsic or extrinsic tumor suppression mechanisms. Immune selection and immune evasion result in the development of advanced breast tumor. Immunosurveillance inhibits or reverses tumor development through killing the tumor cells. Protumorigenic inflammation accompanied advanced breast tumor promotes immune evasion and suppresses effective immunosurveillance.