The Role of Cytokines in Breast Cancer Development and Progression

Marcela Esquivel-Velázquez,¹ Pedro Ostoa-Saloma,¹ Margarita Isabel Palacios-Arreola,¹
Karen E. Nava-Castro,² Julieta Ivonne Castro,² and Jorge Morales-Montor¹

Cytokines are highly inducible, secretory proteins that mediate intercellular communication in the immune system. They are grouped into several protein families that are referred to as tumor necrosis factors, interleukins, interferons, and colony-stimulating factors. In recent years, it has become clear that some of these proteins as well as their receptors are produced in the organisms under physiological and pathological conditions. The exact initiation process of breast cancer is unknown, although several hypotheses have emerged. Inflammation has been proposed as an important player in tumor initiation, promotion, angiogenesis, and metastasis, all phenomena in which cytokines are prominent players. The data here suggest that cytokines play an important role in the regulation of both induction and protection in breast cancer. This knowledge could be fundamental for the proposal of new therapeutic approaches to particularly breast cancer and other cancer-related disorders.

Introduction

THE PROCESS BY WHICH breast cancer is initiated is unknown, for which several hypotheses have emerged. Inflammation has been proposed to mediate the initiation and promotion of tumors, angiogenesis, and metastasis (Grivennikov and others 2010). Inflammatory cells are attracted by oncogenic changes, hypoxia, cytokines, and chemokines, among other factors. Inflammation in a tumor microenvironment comprises infiltrating immune cells and activated fibroblasts that secrete cytokines, chemokines, and growth factors to which the tumor responds (Coussens and Werb 2002; Grivennikov and others 2010).

Obesity can result in an inflammatory environment that can contribute to tumorigenesis. Menopause and increased age are also associated with systemic inflammation (Bruunsgaard and others 2001; Pfeilschifter and others 2002). In turn, cancer therapy can effect an inflammatory tumor microenvironment by provoking extensive tumor cell death (Baumgarten and Frasar 2012).

Several cytokines regulate the inflammatory tumor microenvironment. Interleukin (IL)-1, IL-6, IL-11, and transforming growth factor- β (TGF- β) stimulate cancer cell proliferation and invasion (Nicolini and others 2006), and cytokine receptor activation and intracellular signaling by NF- κ B accelerate tumor progression (Karin and Greten 2005; Hsing and others 2012).

Transforming growth factor- β

TGF- β is the most extensively studied cytokine in breast cancer. TGF- β belongs to the TGF- β superfamily and is a major regulator of many processes, including proliferation, differentiation, migration, immunity, and apoptosis. TGF- β has dual functions in tumor progression. As a tumor suppressor, it has antiproliferative effects in the early stages of tumorigenesis, but tumor cells in later stages evade this effect and progress in response to TGF- β (Fig. 1) (Joshi and Cao 2010; Band and Laiho 2011; Inman 2011; Meulmeester and Ten Dijke 2011; Zu and others 2012). TGF- β , T β RII (the receptor required for TGF- β signaling), and phospho-Smad2 expression are associated with earlier age of onset and aggressive tumor characteristics (Figueroa and others 2010).

In the early stages of cancer, TGF- β causes cell-cycle arrest, particularly in epithelial, endothelial, and hematopoietic cells (Massagué 2008; Heldin and others 2009; Tian and Schiemann 2010; Allington and Schiemann 2011), inhibiting cyclin-dependent kinases by downregulating c-Myc and ID1 and upregulating CDK inhibitors, including p15 and p21 (Donovan and Slingerland 2000; Feng and others 2002; Perk and others 2005; Glasgow and Mishra 2008; Massagué 2008; Juárez and Guise 2010). TGF- β also restricts estrogen receptor (ER) α -mediated proliferation (Ewan and others 2005; Band and Laiho 2011). Many triple-negative human breast cancer cell lines, including MDA-MB-231,

¹Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, México City, México.

²Centro de Investigación Sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, SSA, Cuernavaca, Morelos, México.

FIG. 1. Role of cytokines in the different stages of breast cancer. This figure resumes the role that different cytokines have on establishment, progression, and metastasis of breast cancer. **(A)** Normal cells can adopt a neoplastic phenotype by the action of IL-6, IL-1, TNF- α , and proinflammatory cytokines, which cause NF- κ B activation and an increase in cyclin D1 in the normal breast cell, resulting in a neoplastic phenotype. **(B)** The proliferation of these cells, at early stages of cancer, is suppressed by TGF- β . However, at later stages, TGF- β promotes proliferation of these cells, tumor progression, and invasiveness. **(C)** Stromal fibroblasts and CAFs are an important source of TGF- β . TGF- β and IL-6 can lead to the initiation of the EMT process, which finally ends in cells that can survive not bonded to other cells and, thus, can migrate to other parts of the body and result in the spreading of the cancer.

BT20, Hs578T, HCC1937, and HCC3153, are resistant to the growth-inhibitory activity of TGF- β (Lin and others 2012). In many cases, the antiproliferative effects of TGF- β are attributed to altered TGF- β signaling due to somatic mutations in components of TGF- β signaling or selective inhibition of cytostatic responses to TGF- β . Mutations in T β R-I are infrequently detected in breast cancers (Imamura and others 2012).

The tumor-promoting effects of TGF- β are complex and entail the expression and translocation of the nuclear factor of activated T cells into the nucleus, stimulating c-Myc expression (Singh and others 2010). TGF- β activates Smad3/4, which, in turn, specifically binds to the *HDM2* promoter and upregulates *HDM2*, destabilizing p53 in human breast cancer (Zu and others 2012).

TGF- β is a mediator of the epithelial-to-mesenchymal transition (EMT), which is categorized into 4 subtypes: type 1, or embryonic and developmental EMT; type 2, or tissue-regeneration and fibrotic EMT; and type 3, or cancer progression and metastatic EMT (Kalluri and Weinberg 2009). Type 3 EMT has been linked to the progression and dissemination of breast cancer. TGF- β generates polarized epithelial cells that alter their epithelial phenotype by downregulating genes which form adherent and tight junctions, remodel the cytoskeleton, and upregulate genes that are associated with cell motility and a mesenchymal phenotype (Heldin and others 2009; Wendt and others 2009; Xu and others 2009; Allington and Schiemann 2011; Zu and others 2012), promoting tumor growth and metastasis (Vincent and others 2009; Voulgari and Pintzas 2009; Wendt and others 2009; Xie and others 2012).

The mechanisms through which TGF- β promotes the EMT are complex. For example, in Wnt signaling, the transcriptional repressor SNAIL1 affects the EMT through its interaction with Smad3 and Smad4, which downregulates CAR, occludin, claudin-3, and E-cadherin in breast epithelial cells (Vincent and others 2009). TGF- β also upregulates TF3, a transcription factor that regulates morphology, EMT marker expression, and cancer-initiating features in breast cells (Yin and others 2010). TGF- β communicates with Wnt, Her2, and FAK, which influence the EMT and breast cancer stem cells (BCSCs), and it promotes the formation of cancer stem cells (Taube and others 2010; Jain and Alahari 2011; Zu and others 2012).

Interleukin-6

Breast cancer cell lines produce IL-6, of which ER-positive cells secrete lower levels than ER-negative cells. IL-6 induces proliferation and a more aggressive phenotype in ER-positive cells (Sasser and others 2007). Fibroblasts from breast tissue also secrete IL-6, which stimulates the growth and invasiveness of MCF-7 cells (Studebaker and others 2008; Baumgarten and Frasor 2012). Further, IL-6 regulates the inducible formation and maintenance of BCSCs (Iliopoulos and others 2011). Through the IL-6 receptor/GP130 complex and STAT3 activation, IL-6 governs the self-renewal of BCSCs (Iliopoulos and others 2009, 2010; Korkaya and others 2011). Overexpression of IL-6 in MCF-7 cells induces the EMT and increases their invasiveness (Sullivan and others 2009).

IL-6 bridges Stat3 and NF- κ B-dependent inflammatory cytokines (eg, IL-1, TNF- α). The initial activation of NF- κ B by inflammatory signals activates a self-reinforcing regulatory circuit that comprises IL-6 and Stat3 and converts a stable normal cellular phenotype into a stable neoplastic phenotype without any change in DNA sequence (Iliopoulos and others 2009), linking tumorigenesis to NF- κ B activation and inflammation (Ernst and Putoczki 2012).

Tumor necrosis factor- α

Tumor necrosis factor (TNF)- α , an inflammatory cytokine that is highly expressed in breast carcinomas (Leek and others 1998), stimulates the proliferation of T47D cells through an NF- κ B-dependent increase in cyclin D1 (Baumgarten and Frasor 2012). Inhibition of NF- κ B and TNF- α is protective against chemically induced breast tumorigenesis (Connelly and others 2011). Further, *in vitro* activation of the TNF- α /NF- κ B axis induces invasive and malignant behavior in breast cancer cells (Balkwill 2009). Chronic expression of TNF- α in breast tumors supports tumor growth (Kamel and others 2012), but the effects of TNF- α *in vitro* differ between breast cancer cell lines. In contrast to its effects in T47D cells, TNF- α induces apoptosis (Donato and Klostergaard 2004); inhibits proliferation; and promotes migration, invasion, and resistance to chemotherapeutic drugs in MCF-7 cells (Goldberg and Schwertfeger 2010), regulating genes and enzymes that mediate estrogen metabolism, leading to higher levels of DNA adducts (Kamel and others 2012). Thus, TNF- α is a necrotic and tumor-promoting factor—in the tumor microenvironment, TNF- α enhances tumor growth and migration, whereas local administration of high doses of TNF- α has robust antiangiogenic and antitumoral effects (Hamed and others 2012).

Interleukin-17

IL-17, a cytokine that is secreted by CD4 and CD8 cells (6–8), is required for the development and tumor-promoting activity of myeloid-derived suppressor cells (MDSCs) in tumor-bearing mice (He and others 2010). TGF- β , IL-6, and IL-23 have been implicated in the initiation of Th17 cell differentiation in mice (Veldhoen and others 2006; Zhou and others 2007; Novitskiy and others 2011).

IL-19, IL-20, TGF- α , and IL-23

IL-19, IL-20, TGF- α , and IL-23 are also involved in breast tumorigenesis and tumor progression. IL-19 provides a microenvironment that is conducive to tumor progression through an autocrine effect, stimulating the proliferation and migration of cancer cells through matrix metalloproteinase (MMP)-2, MMP-9, IL-1 β , IL-6, TGF- β , CXCR4, and fibronectin (Hsing and others 2012). Studies *in vitro* have demonstrated that IL-19 induces the proliferation of the MCF-7 and Hs578T human breast carcinoma cell lines and of the 67NR and 4T1 murine breast cancer lines (Hsing and others 2012). IL-20 enhances the proliferation and migration of cancer cells and creates a microenvironment that fosters tumor progression by upregulating MMPs and cathepsins (Hsu and others 2012). In turn, IL-23 affects inflammation and angiogenesis in the tumor microenvironment while tempering CD8⁺ T-cell infiltration (Langowski and others

2006). TGF- α promotes tumor growth and progression through an autocrine/paracrine loop that involves EGFR (Ziober and others 1993; Humphreys and Hennighausen 2000; Booth and Smith 2007).

Adipokines and Breast Cancer

Obesity is a significant risk factor for breast cancer development. Obesity is associated with elevated levels of proinflammatory cytokines in adipose tissue and in circulation, which establishes a low-grade, chronic inflammatory state. One hallmark of obesity-associated inflammation is the recruitment of macrophages into adipose tissue. Macrophages and adipocytes produce inflammatory factors, such as adipokines and cytokines (Ouchi and others 2011), leading to the activation of NF- κ B in adipose tissue and the liver (Cai 2009; Baumgarten and Frasor 2012).

Adipokines (cytokines that are secreted by adipose tissue), such as leptin, adiponectin, IL-6, TNF- α , and IL-1, mediate inflammatory diseases and obesity (Tilg and Moschen 2006). Glucose and fatty acids enhance the ability of adipocytes to produce factors, including IL-8, RANTES, and IGF-1, that influence cancer cell phenotypes. Stromal vascular fraction cells and differentiated adipocytes from obese individuals release more IGF-1 than those from lean individuals, suggesting that obesity favors breast cancer cell growth (D'Esposito and others 2012). Leptin synthesis and plasma levels increase with obesity (Wu and others 2009; Barone and others 2012).

In breast biopsies, IL-1 is 1 of the 5 cytokines (with IL-2, IL-4, IL-10, and G-CSF) that are overexpressed in ductal breast carcinoma but undetected in normal breast tissue (Pantschenko and others 2003; Chavey and others 2007). The production of IL-1, even in small amounts, induces potent secondary responses, in part through its ability to elicit the secretion of other cytokines, chemokines, adhesion molecules, and receptors for cytokines from various cells (Dinarello 1996). IL-1 has been linked to the proliferation, invasion, angiogenesis, and inhibition of apoptosis in cancer cells (Apte and others 2006; Lewis and others 2006). IL-1 and IL-8 induce breast cancer progression by enhancing metastasis and cachexia (Wolf and others 2001; Veldhoen and others 2006). IL-1 family members also modulate the activity of estrogens and their receptors—IL-1 expression is primarily observed in ER-negative breast tumors (Miller and others 2000).

IL-1-induced proliferation is mediated by the estrogen-synthesizing enzymes P450 aromatase and steroid sulfatase, which generate bioactive estrogens. IL-1 enhances aromatase activity in SK-BR3 cells and steroid sulfatase activity in MCF-7 cells by 120% and 130%, respectively (Honma and others 2002). IL-1 receptors are expressed in estrogen-dependent (MCF-7, ZR75-1) and estrogen-independent cell lines (MDA-MB 231) (Pantschenko and others 2003). In contrast, IL-1 α , IL-1 β , and IL-1ra are preferentially expressed in highly malignant and invasive mammary cell lines (BT 20, BT 549, HS 578T, and MDA-MB 231) and not in the MCF-7, T47-D, ZR75-1, or SKBR-3 lines (Singer and others 2003). TNF and IL-6 upregulate aromatase in the tumor microenvironment, which might stimulate the growth of ER-positive cancers (Cleary and Grossmann 2009). TNF and IL-6 expression correlates with aromatase levels in breast cancer but not in the adjacent normal breast tissue (Irahara and others 2006).

Leptin, a proinflammatory cytokine (Otero and others 2006), is secreted primarily by adipocytes, although breast cancer cell lines produce leptin in a process that is regulated by IL-1 (Faggioni and others 1998; O'Brien and others 1999; Iguchi and others 2001). Leptin and its receptor, ObR, are expressed in normal breast epithelial cell lines and breast cancer cell lines (O'Brien and others 1999; Hu and others 2002; Laud and others 2002). Leptin is expressed in ductal breast carcinoma but not in healthy breast tissues, and its expression correlates with the stage of invasion (Caldefie-Chézet and others 2005; Jardé and others 2008). Further, ObR is present in human breast carcinoma but not in normal breast tissue (Perrier and others 2009). Leptin upregulates aromatase in MCF-7 cells through a greater binding of AP-1 to promoters (Catalano and others 2003). In breast cancer, increased AP-1 levels correlate with high expression of several cytokines, including IL-1 β (Chavey and others 2007).

ObR expression is associated with ER and tumor size (Jardé and others 2008), implicating an interaction between the leptin and estrogen systems to promote breast carcinogenesis. Several immune cells express ObRs, which might render them responsive to leptin (Martín-Romero and others 2000; Caldefie-Chézet and others 2001; Fujita and others 2002; Caldefie-Chézet and others 2003; Zhao and others 2003). In rats, elevated IL-1 β concentrations in peripheral blood increase leptin levels and total body fat mass and stimulate the growth of mammary epithelium (Reichlin and others 2000).

Cancer cells organize their microenvironment, recruiting stromal fibroblasts in the desmoplastic reaction; these fibroblasts and α -smooth muscle actin-positive myofibroblasts (MFs)—collectively termed carcinoma-associated fibroblasts (CAFs)—are reprogrammed to produce growth factors, cytokines, and extracellular matrix (ECM)-remodeling proteins that act in an autocrine and paracrine manner to support tumor proliferation and invasion into surrounding tissues (Orimo and Weinberg 2006; Casey and others 2008; Kojima and others 2010; Barone and others 2012; Zu and others 2012) (Fig. 1).

During tumor progression, TGF- β stimulates the progressive conversion of mammary fibroblasts into CAF MFs, promoting tumor progression (Casey and others 2008; Kojima and others 2010; Shanguan and others 2012; Zu and others 2012). Mesenchymal stem cells (MSCs) are a source of CAFs that are phenotypically similar to MFs (Ostman and

Augsten 2009). When injected with cancer cells, MSCs promote the growth and metastasis of cancers (Karnoub and others 2007; Shanguan and others 2012). MSCs are recruited to developing tumors, where they increase breast cancer cell motility, invasion, and metastatic potential by secreting chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES) (Karnoub and others 2007).

In breast tumor development, leptin is a determinant of the tumor-promoting activity of CAFs in normal and K303R-mutated ER α -expressing breast cancer cells, demonstrating that cross-talk exists between breast cancer cells and “educated” CAFs which drives tumor progression through leptin signaling (Barone and others 2012). Leptin, secreted from CAFs, binds to its receptor; activates K303R-ER α ; and stimulates the proliferation, migration, and invasiveness of K303R-ER α -expressing breast cancer cells. In turn, K303R cells release factors, such as EGF, that induce CAFs to enhance leptin secretion, which might establish a positive feedback loop between cancer and stromal cells to further support breast tumor progression (Barone and others 2012). In addition to CAFs, adipose stromal cells effect invasion and metastasis by MCF-7 cells—a phenotype that is driven by IL-6 (Walter and others 2009; Baumgarten and Frasar 2012).

Adiponectin, another adipokine, might also be involved in breast cancer development. Adiponectin has antiproliferative effects on human breast cancer cells through the initiation of apoptosis and inhibition of the cell cycle (Kang and others 2005; Dieudonne and others 2006; Perrier and others 2009) (Fig. 2).

Observational evidence suggests that the risk for breast cancer decreases with intentional weight loss. Cancer incidence rates have declined in patients who have undergone bariatric surgery, whereas surgery is associated with an 83% lower risk of incident breast cancer. The ratios of percentage weight loss to percentage change in estradiol and SHBG suggest that a 10% loss in body weight affects a reduction in free estradiol levels by at least one-third. Further, a 10% loss in weight is expected to produce decreases in inflammatory markers by one-third. TNF- α and IL-6 levels also decrease with intentional weight loss, albeit to a lesser extent (Byers and Sedjo 2011). Thus, intentional weight loss might be an effective prophylactic method of reducing the risk of breast cancer or a secondary treatment that improves the prognosis of breast cancer patients.

FIG. 2. Role of adipokines and other cytokines in the progression of breast cancer. Obesity is associated with elevated levels of proinflammatory cytokines in adipose tissue and in circulation, which establishes a low-grade, chronic inflammatory state. Fat cells and macrophages (MO) associated with them produce adipokines and cytokines to which breast cancer cells respond by increasing the expression of P450 aromatase and steroid sulfatase, which, in turn, generate bioactive estrogens; and by producing several cytokines that act in an autocrine fashion. These responses lead to cancer progression and metastasis.

Cytokines and Angiogenesis

Many cytokines participate in angiogenesis, which is essential for tumor growth and progression. TGF- β enhances tumor vascularity by regulating the expression of cathepsin G, vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein (MCP)-1 and promotes immune evasion and ECM degradation (Wilson and others 2010; Zu and others 2012). Breast cancer tumor cells overexpress bcl-2 and sFas to ensure their outgrowth and survival, but this coincides with the activation of regulatory mechanisms, such as increased IL-8, TNF- α , LPO, and NO, which attempt to halt tumor cell growth by inducing apoptosis. Ultimately, an imbalance in these mechanisms results in tumor progression, because IL-8, TNF- α , and NO are also angiogenic stimulators (Hamed and others 2012; Kamel and others 2012).

Breast cancer tissues express high concentrations of IL-8 compared with normal tissue (Snoussi and others 2006), which correlates with angiogenesis (Zuccari and others 2012). IL-8 that is secreted by tumor cells enhances endothelial cell proliferation, survival, and MMP production (Hamed and others 2012). In contrast, IL-24, a member of the IL-10 family, suppresses tumor vascularization (Xie and others 2008; Hsu and others 2012).

Chronic inflammation can also lead to angiogenesis, because tumor-infiltrating lymphocytes secrete copious amounts of proinflammatory cytokines, such as IL-6, IL-1 α , IL-1 β , tumor necrosis factor- α , and oncostatin M, which are believed to upregulate COX-2, which, in turn, increases VEGF expression in tumor cells, promoting angiogenesis (Angelo and Kurzrock 2007). Inflammatory events can also lead to breast cancer metastasis. Further, hypoxic tumor conditions induce COX-2 expression, which activates hypoxia-inducible factor-1 α (HIF-1 α), a transcription factor that activates angiogenesis-promoting genes, such as *veg*f and *cox*-2 (Jung and others 2003; Angelo and Kurzrock 2007) (Fig. 3).

Inflammatory breast cancer exhibits a higher expression of proangiogenic molecules, such as angiopoietin-1, VEGF, and VEGF receptors than noninflammatory breast cancer (Van der Auwera and others 2004; Angelo and Kurzrock 2007).

Cytokines and Breast Cancer Metastasis

Metastasis of breast cancer, such as tumorigenesis and tumor progression, has many mechanisms. Some cytokines in breast cancer, such as TGF- β and IL-6, can promote tumor metastasis through the EMT (Fig. 1), a process that is characterized by reduced expression of E-cadherin and upregulation of markers, such as vimentin and N-cadherin (Culig 2011). CAFs mediate the EMT, producing high amounts of TGF- β (Yilmaz and Christofori 2009; Patel and others 2012).

TAMs are also linked to metastasis, secreting tumor cell migration-stimulating factors, such as CXCL12, IL-6, and TNF (Allavena and others 2008). Macrophage recruitment might be necessary for the progression of breast tumors to a metastatic state, as suggested by studies on a polyoma middle T oncogene (PyMT) mouse model of mammary cancer (Baumgarten and Frasor 2012). Moreover, TAMs might contribute to tumor progression, because TAMs produce estrogen and as conditioned media from TAM cultures stimulate ER-positive breast cancer cells growth (Fig. 2) (Mor and others 1998; Baumgarten and Frasor 2012).

FIG. 3. Cytokines involved in angiogenesis. The inflammatory infiltrate that is usually found in breast tumors produce IL-6, IL-1 α , and IL-1 β , which upregulate COX-2, which, in turn, increases VEGF expression in tumor cells promoting angiogenesis. IL-8, TNF- α , TGF- β , and NO, produced by tumor cells, are angiogenic stimulators. TGF- β regulates the expression of cathepsin-G, VEGF, and MCP-1, promoting extracellular matrix degradation and angiogenesis. IL-24 suppresses tumor vascularization.

Colony-stimulating factor 1 (CSF-1) might mediate the recruitment of macrophages to breast tumors (Lin and others 2001). The proto-oncogene *c-fms* encodes the only known receptor (CSF-1R) for CSF-1 (Sherr and others 1985; Dai and others 2002). The expression of CSF-1 and its receptor in neoplastic epithelial breast cancer cells correlates well with a poor prognosis and is predictive of ipsilateral recurrence (Scholl and others 1994; Maher and others 1998; Kluger and others 2004). CSF-1 promotes metastasis, stimulates angiogenesis, and participates in a paracrine loop with EGF to spur tumor cell invasion in mouse models (Lin and others 2001; Aharinejad and others 2002; Aharinejad and others 2004; Wyckoff and others 2004).

Breast cancer cell lines consistently express CSF-1 and CSF-1R, which sustains the proliferation in SKBR3 and MDAMB468 breast cancer cells through ERK1/2 activation, stimulating c-Jun and upregulating c-myc and cyclin D1. CSF-1R is not overexpressed or amplified in breast cancer cells compared with human monocytes, suggesting that the oncogenic potential of CSF-1R is attributed to its coexpression with CSF-1 (Morandi and others 2011).

TNF promotes tumor cell invasion, as evidenced in *in vitro* experiments, upregulating several genes that are associated with proliferation, invasion, and metastasis (Yin and others 2009; Baumgarten and Frasor 2012). IL-1 also effects the migration and metastasis of ER-positive cancer cells (Wang and others 2005; Franco-Barraza and others 2010), altering their morphology to assume more of a fibroblast-like appearance and reorganizing the actin cytoskeleton, increasing motility and MMP-9 activity (Duffy and others 2000;

Baumgarten and Frasor 2012). Greater IL-8 expression in breast cancer patients correlates with metastasis (Simeone and others 2007).

IL-19 induces the migration of breast cancer cells, such as Hs578T and 4T1, by upregulating CXCR4, MMP-2, MMP-9, TGF- β , IL-1 β , and IL-6—factors that are involved in tumor progression and metastasis. Overexpression of IL-19 in 67NR cells, which usually have low endogenous IL-19 levels, and MCF-7 cells stimulates their proliferation and migration, enabling them to form larger tumors and metastatic micronodules in the lung on injection into mice (Hsing and others 2012). IL-20 *in vitro* upregulates MMP-9, MMP-12, cathepsin K, and cathepsin G and enhances the proliferation and migration of breast cancer cells. IL-20 is highly expressed in breast cancer bone metastases (Hsu and others 2012).

MSC-derived monocyte chemotactic protein-1 (MCP-1/CCL2) and IL-17B promote breast cancer cell migration (Molloy and others 2009; Goldstein and others 2010; De Luca and others 2012). MSCs are a source of factors, such as VEGF and IL-6, that, in addition to promoting angiogenesis, induce breast cancer cell migration and invasion, (Beckermann and others 2008; De Luca and others 2011; De Luca and others 2012). VEGF stimulates the invasion of breast cancer cells by activating MAPK and PI3K/AKT signaling (Price and others 2001).

Hypoxia, characterized by abnormally low levels of oxygen in cells, is a feature of most solid tumors, including breast cancer. This condition orchestrates a series of effects principally regulated by the family of HIFs. HIFs, when translocated to the nucleus in response to low oxygen, induce the expression of a series of factors in cells related to proliferation and survival, metabolism, invasion and metastasis, angiogenesis, pH regulation, and maintenance of stem cells. Between these factors, several cytokines can be found: for example, TGF- α , Igf-2, and Igf-Bp2 (Favaro and others, 2011). In the case of breast cancer, hypoxic conditions induce cytokine and growth factor secretion from MSCs, such as TGF- β 1, TGF- β 2, and TGF- β 3, which affects the growth, motility, and invasiveness of breast cancer cells (Hung and others 2012a, 2012b). Evenmore, TGF- β and hypoxia (through HIF-1 α) in parallel drive tumor bone metastases in breast cancer by the regulation of a common set of genes (*CTGF*, *OPN*, *MMP-1*, *IL-6*, and *IL-8*, among others) and additively increment the expression of prometastatic factors VEGF and CXCR4 (Dunn and others, 2009). TGF- β induces the invasiveness of noncarcinogenic epithelial MCF-10A1 (M1) cells and RAS-transformed M1-derived MCF-10AneoT (M2) cells in spheroid assays (Naber and others 2011). Further, levels of TGF- β 1 and TGF receptor and cell invasiveness correlate inversely with junctional adhesion molecule-A (JAM-A) expression in breast cancer cell lines (Arteaga and others 1988; Koli and Arteaga 1997; Naik and others 2008). Downregulation of JAM-A due to TGF- β 1 involves the TGF- β /Smad and TGF- β /p54 JNK pathways, inducing breast cancer cell invasion (Wang and Lui 2012).

TGF- β 1 mediates an EMT-like process, which, in turn, can induce cancer stem cell-like properties in HMLE cells. HMLER cells, which are human primary normal mammary epithelial cells that have been immortalized using hTERT and SV40 large T antigen and H-Ras to render them tumorigenic (Elenbaas and others 2001; Mani and others

2008), potentially lead to early dissemination of breast cancer cells, which can sometimes survive at sites of dissemination and may outgrow after a long latency of years (Podsypanina and others 2008; Sabe 2011).

Inflammatory breast cancer has greater metastatic potential than noninflammatory breast cancer (Van der Auwera and others 2004; Angelo and Kurzrock 2007).

Cytokines, Immunosuppression, and Evasion in Breast Cancer

Breast cancer cells have mechanisms that enable them to grow and progress. As discussed, cytokines are important mediators of tumor growth and metastasis, some of which also help the tumor evade immune responses and benefit from them. For instance, TGF- β binds to MDSCs, causing them to suppress natural killer (NK) cells. TGF- β also influences regulatory T-cell activity (Yoshimura and others 2010) through a neuropilin-1 (Nrp1)-mediated mechanism and supports breast cancer growth (Glinka and Prud'homme 2008; Zu and others 2012).

IL-10 has not only been implicated in the immunosuppression in breast cancer, but it is also involved in the anti-tumor response. IL-10 is a potent anti-inflammatory cytokine that inhibits gene expression, cytokine synthesis by T cells and macrophages, and their antigen presentation. IL-10 suppresses the production of IL-1 α , IL-1 β , TNF- α , IL-6, IL-8, IL-12, IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), MIP-1 α , RANTES, leukemia-inhibiting factor, and itself (Moore and others 1993; Hamidullah and others 2011).

TAMs are a significant source of IL-10 in the tumor microenvironment. TAMs have an immunosuppressive phenotype, characterized by the release of IL-10, likely in response to S1P from dying cancer cells through a complex signaling network that requires S1PR/src-dependent trafficking of TRKA to the plasma membrane in primary human macrophages, on which autocrine NGF induces PI3K/AKT signaling (Weigert and others 2007).

Tumor-associated plasmacytoid dendritic cells (TApDCs) affect immune tolerance through tumor-associated regulatory T-cell expansion and differentiation of IL-10-secreting T cells. The selective suppression of IFN- α production gives TApDC the unique ability to sustain FoxP3⁺ Treg expansion, contributing to immune tolerance by the tumor and poor clinical outcomes (Sisirak and others 2012).

Moreover, tumor cell lines which are cultured *in vitro* express IL-10, suggesting that IL-10 establishes an immune-suppressive tumor microenvironment. However, overexpression of IL-10 in tumor cells that have been transplanted in mice causes tumors to be rejected, implicating CD8⁺ T cells, NK cells, or IL-10 (Zheng and others 1996; Moore and others 2001; Mumm and others 2011).

Cytokines as Prognostic Factors in Breast Cancer

In addition to their effects on tumor progression, the levels of several cytokines have been correlated with tumor stage, survival, and malignancy, rendering them potential prognostic factors.

High levels of TGF- β have been linked to worse survival in breast cancer patients, and plasma TGF- β levels might be

predictive of local and distant metastasis (Grau and others 2008; Brier and others 2009; Ivanović and others 2009; Yu and others 2010; Zu and others 2012). Loss of Wnt5a, which is directly regulated by TGF- β , is associated with early relapse of invasive breast cancer, increased metastasis, and poor survival in breast cancer patients (Serra and others 2011). Higher circulating levels of TGF- β 2 correlate with nonpremenopausal status, infiltrating ductal carcinoma, higher histological grade, presence of vascular permeation and lymphocytic infiltration, and longer relapse-free survival, making them likely to be used as a marker of favorable prognosis (Dave and others 2011).

Reduced and increased expression of TGF- β 3 in breast tumor biopsies is associated with a poor and a good prognosis, respectively (van de Vijver and others 2002). Similarly, lower TGF- β 3 mRNA levels correlate with higher tumor grade (van de Vijver and others 2002; Miller and others 2005; Ivshina and others 2006; Sotiriou and others 2006; Desmedt and others 2007). Conversely, higher circulating levels of TGF- β 3 and TGF- β 3-receptor complexes are linked to the presence of lymph node metastases (Laverty and others 2009). Further, TGF- β 3 is central to the parity-induced protection against breast cancer, which occurs in women who give birth before the age of 24 years. Parity induces chronic upregulation of TGF- β 3 (D'Cruz and others 2002; Laverty and others 2009).

IL-1 family members have prognostic value in breast cancer. IL-1 is expressed particularly in ER-negative breast tumors. Levels of IL-1 in the serum and tumor correlate with invasiveness and a poor prognosis (Goldberg and Schwertfeger 2010). Elevated levels of IL-1 β are associated with invasiveness and aggressiveness of breast cancer and higher tumor grade (Jin and others 1997; Chavey and others 2007). High IL-1 receptor antagonist (IL-1ra) levels and low levels of IL-1 at the tumor site are linked to a good prognosis in breast cancer—in the healthy population, individuals with low serum IL-1ra concentrations have higher levels of adiponectin (Rafiq and others 2007); these correlate with increased expression of ERs (Pantschenko and others 2003). Low serum levels of adiponectin are a risk factor for the development of breast cancer in postmenopausal women (Miyoshi and others 2003; Hou and others 2007; Perrier and others 2009).

Moreover, serum IL-6 levels are significantly higher in breast cancer patients than in healthy women, and increased IL-6 levels correlate with poorer survival and diminished response to endocrine therapy in patients with metastatic breast cancer (Zhang and Adachi 1999; Knüpfer and Preiss 2007; Culig 2011; Baumgarten and Frasor 2012; Liu and others 2012a). Plasma from benign breast tumor patients have significantly elevated levels of IL-6 compared with normal controls (Nariša and others 2011). Patients with high IL-6 concentrations have worse responses to chemotherapy and hormone therapy (Zhang and Adachi 1999). IL-6 levels are lower in breast cancer patients who respond better to therapy (Zhang and Adachi 1999; Guo and others 2012). Nevertheless, IL-6 levels have been reported as positive and negative predictors in breast cancer (Knüpfer and Preiss 2007).

IL-19 expression in breast cancer tissue is associated with a higher mitotic rate, advanced tumor stage, metastasis, and worse disease-specific and metastasis-free survival (Hsing and others 2012), implicating it in progression of the tumor.

In breast cancer, IL-8 is associated with lymph node-positive status, higher stage, and lack of hormone receptors (Zuccari and others 2012). Serum IL-8 has been linked to accelerated clinical progression, greater tumor load, and the presence of lymph node and liver metastases (Benoy and others 2004; Culig 2011). Patients with HER-2/neu + tumors have increased serum IL-8 levels versus those with HER-2/neu- tumors (Vazquez-Martin and others 2007). In contrast, patients with local recurrence or metastases have lower IL-8 levels (Zuccari and others 2012). Plasma IL-8 levels are higher in stage III and IV breast cancer patients compared with stage I and II (Hamed and others 2012).

Circulating TNF levels correlate with higher tumor stage and lymph node metastasis (Sheen-Chen and others 1997). TNF levels are greater in invasive breast cancer tissue than in benign tissue (Miles and others 1994; Baumgarten and Frasor 2012). IL-13 levels show a similar correlation of TNF levels and clinicopathological characteristics in breast cancer patients (Srbovic and others 2011). Higher TNF- α -expressing populations correlate with increasing tumor grade and node involvement (Kamel and others 2012). Similarly, TNF- α plasma levels are elevated in stage II, III, and IV breast cancer patients versus those with stage I and healthy controls (Hamed and others 2012).

IL-10 concentration is frequently higher in the serum of breast cancer patients compared with normal subjects. Elevated IL-10 might inhibit tumor growth by suppressing IL-6 production, based on the inverse correlation between IL-6 and IL-10 levels in cancer patients (Kozłowski and others 2003). IL-10 is overexpressed in ER-negative versus ER-positive breast tumors (Chavey and others 2007). A correlation between IL-10 level and clinical stage has also been reported (Merendino and others 1996)—metastatic disease is associated with higher IL-10 levels than nonmetastatic disease, which might contribute to impaired immunosurveillance, favoring tumor development.

IL-20 is associated with advanced tumor stage, greater tumor metastasis, poor clinical outcome, higher mitotic rate, and worse survival (Hsu and others 2012). Elevated IL-23 levels in breast cancer patients correlate with shorter overall survival (Gangemi and others 2012).

In contrast, higher circulating soluble IL-2R levels appear to be a favorable prognostic indicator (Nicolini and others 2006; Gangemi and others 2012) (Table 1).

Cytokines and Quality of Life in Breast Cancer Patients

Quality of life is a significant issue in breast cancer patients and survival. Patients experience pain, sleep disturbances, and fatigue, even after treatment has ended. More than 54% of patients develop moderate to severe pain during the treatment trajectory (van den Beuken-van Everdingen and others 2007; Starkweather and others 2013).

Increasing evidence suggests that modulation of immune activation through a greater secretion of proinflammatory cytokines accelerates the development of distressing symptoms in women with breast cancer (Lyon and others 2008; Reyes-Gibby and others 2008; Starkweather and others 2013).

Increased levels of IL-1 and IL-6 are associated with pain and sleep disturbances in breast cancer survivors (Collado-Hidalgo and others 2006; Starkweather and others 2013). A significant rise in plasma IL-1ra is also linked to post-treatment

TABLE 1. CYTOKINES' UTILITY FOR BREAST CANCER PROGNOSIS AND SURVIVAL

<i>Cytokine</i>	<i>Location</i>	<i>Levels</i>	<i>Prognosis</i>	<i>Impact on survival</i>	<i>References</i>
TGF- β	Tumor	$\uparrow$	Is predictive of local and distant metastases. Loss of Wnt5a, regulated by TGF- β , is associated with early relapse and metastases	Worse survival	Grau and others (2008); Ivanović and others (2009); Yu and others (2010); Zu and others (2012)
TGF- β 2	Serum, tumor	$\uparrow$	Favorable: In circulation, higher levels correlate with later relapse. TGF- β 2 mRNA expression correlates with early relapse in advanced stage than in early stage of breast cancer Unfavorable: Higher transcript levels in tissue is a marker of unfavorable prognosis	Longer relapse-free survival. mRNA levels correlate with increased survival in early breast cancer than in advanced stage	Dave and others (2011)
TGF- β 3	Tumor	$\uparrow \downarrow$	Reduced expression correlates with poor prognosis and higher tumor grade, while increased expression is indicative of good prognosis	Not determined	Desmedt and others, (2007); Ivshina and others (2006); Miller and others (2005); Sotiriou and others (2006); van de Vijver and others (2002)
TGF- β 3	Serum	$\uparrow$	Higher TGF- β 3- TGF- β 3 receptor complexes are linked to lymph node metastases: poor prognosis Nonetheless, upregulation of this cytokine is involved in the parity-induced protection against breast cancer in women who gave birth before the age of 24 years	Not determined	D'Cruz and others (2002); Laverty and others (2009)
IL-1 and IL-1B	Serum, tumor	$\uparrow$	High in tumor and circulation: poor prognosis, more aggressive and invasive tumor. High IL-1ra and low IL-1 at tumor site: good prognosis	Not determined	Chavey and others (2007); Goldberg and Schwerfeger (2010); Jin and others (1997); Rafiq and others (2007)
IL-6	Serum	$\uparrow$	Poor prognosis: diminished response to endocrine therapy and to chemotherapy Lower levels correlate with better response to therapy: good prognosis	Worse survival	Baumgarten and Frasar (2012); Culig, (2011); Knüpfer and Preiss (2007); Liu and others (2012); Zhang and Adachi (1999)
IL-19	Tumor	$\uparrow$	Associated with higher mitotic rate, advanced tumor stage, and metastasis: poor prognosis	Worse metastasis-free survival	Hsing and others (2012)
IL-8	Tumor	$\downarrow$	Low levels are associated with lymph node-positive status, lack of hormone receptors, accelerated clinical progression, and metastasis: poor prognosis.	Increased risk of death	Culig (2011); Zuccari and others (2012)
TNF and IL-13	Serum	$\uparrow$	Higher levels correlate with higher tumor stage and lymph node metastasis	Not determined	Sheen-Chen and others (1997); Srabovic and others (2011)
IL-10	Serum	$\uparrow$	May inhibit tumor growth by suppressing IL-6. However, higher levels of IL-10 correlate with metastatic disease: poor prognosis	Not determined	Kozłowski and others (2003); Merendino and others (1996)
IL-20	Tumor	$\uparrow$	Associated with advanced tumor stage, metastasis, and poor clinical outcome: poor prognosis	Worse survival	Hsu and others (2012)
CSF-1	Tumor	$\uparrow$	Expression in tumor correlates with ipsilateral recurrence of breast cancer: poor prognosis	Not determined	Maier and others (1998); Scholl and others (1994); Kluger and others (2004)
soluble IL-2R	Serum	$\uparrow$	Good prognosis	Not determined	Gangemi and others (2012); Nicolini and others (2006)
IL-1B	Tumor	$\uparrow$	Correlates with invasiveness, aggressiveness, and higher tumor grade: poor prognosis	Not determined	Chavey and others (2007); Jin and others (1997)

Different cytokines are listed in this table along with their prognostic values in breast cancer. The location in which each cytokine was evaluated is also indicated as well as their impact on survival.

fatigue in breast cancer survivors (Bower and others 2002; Perrier and others 2009). Similarly, IL-17, IL-13, and CRP levels are higher in women who experience pain, greater pain interference, depression, and sleep disturbances (Starkweather and others 2013). Further, VEGF and soluble intercellular adhesion molecule-1 (sICAM-1) levels are associated with fatigue in patients who are undergoing chemotherapy (Mills and others 2005), as are elevated levels of IL-1RA, soluble tumor necrosis factor receptor type II (sTNF-RII), neopterin, and soluble IL-6 receptor, which have been correlated with fatigue in breast cancer patient survivors at 5 years after diagnosis (Karayiannakis and others 2001; Bower and others 2002; Collado-Hidalgo and others 2006; Berger and others 2012).

CRF might be the pathway at which several systems converge, including the central nervous system, immunoregulatory pathways, and the neuromusculoskeletal and cardiopulmonary systems. The physiological and immunological systems, which control inflammatory pathways, might be involved in CRF (Harvey and others 2009). Moreover, sleep problems have been associated with CRF, depression, and poorer overall quality of life (Lis and others 2008; Schultz and others 2011; Berger and others 2012). Sleep regulatory functions can also be affected by cytokines, such as IL-1, IL-6, and TNF- α (Vgontzas and others 1997; Opp 2005; Raison and others 2010; Liu and others 2012b).

Cytokines and Breast Cancer Treatment

Based on their function in breast cancer development, cytokines are attractive targets for new treatments. Further, cytokines can potentiate or impair the efficacy of current breast cancer therapies. For instance, in the presence of IL-1, the selective ER modulator (SERM) 4-hydroxytamoxifen (4-OHT) activates, rather than represses, the transcription of ER target genes. IL-1 displaces an inhibitory complex that contains NCoR from ER target gene promoters, inhibiting their response to 4-OHT (Zhu and others 2006). Thus, IL-1 might regulate ER activity and responsiveness to endocrine therapy (Baumgarten and Frasor 2012).

TNF- α promotes chemotherapeutic resistance in MCF-7 cells through upregulation of ABCG2, an ATP-binding cassette transporter that effluxes chemotherapeutic drugs from cancer cells (Krishnamurthy and Schuetz 2006; Mossaffa and others 2009; Pradhan and others 2010; Baumgarten and Frasor 2012; Malekshah and others 2012). TGF- β signaling also affects the resistance of breast cancer cells to DNA-damaging chemotherapeutic agents (Yu and others 2010; Zu and others 2012), and it might also induce immunosuppression and lead to resistance and relapse in breast cancer (Joffroy and others 2010; Zu and others 2012).

IL-6 and IL-8 are also related to multidrug resistance in breast cancer cells. Only breast cancer cells that are sensitive to drugs do not express IL-6, whereas multidrug-resistant breast cancer cells produce high levels of IL-6 (Guo and others 2012). Neutralization of IL-6 and IL-8 with antibodies significantly enhances the sensitivity of resistant MCF-7 cells to drugs, and their overexpression increases the resistance of MCF-7/Sensitive cells to chemotherapeutic drugs. Further, IL-6 and IL-8 can be induced by chemotherapeutic drugs (Shi and others 2012), which can lead to multidrug-resistant cells.

IL-6 can mediate trastuzumab (anti-HER2/neu mAb) resistance in breast cancer cells by activating an IL-6-dependent inflammatory feedback loop that causes the expansion of CSCs. IL-6 might induce the CSC phenotype in non-CSC cells. Long-term trastuzumab treatment generates highly enriched CSCs that have an EMT phenotype, secreting over 100 times more IL-6 than parental cells. Blocking this IL-6 loop with an antibody against IL-6 receptor interrupts this inflammatory feedback mechanism and decreases the CSC population, resulting in lower tumor growth and metastasis (Korkaya and others 2012).

As therapeutic agents, GM-CSF and granulocyte colony-stimulating factor (G-CSF) have been evaluated with regard to their value in preventing or reducing the incidence of febrile neutropenia (FN) due to high-dose intensive cytotoxic chemotherapy. FN often requires hospitalization and intravenous antibiotics. Peter and others (2013) performed a meta-analysis of several clinical trials and demonstrated that CSF is beneficial in the prevention of NF. However, CSF can cause adverse events, such as bone pain and injection-site reactions. No conclusions could be drawn from this meta-analysis, as the studies had a few patients, varying definitions, and unclear measurements of trial outcomes.

IFNs, IL-2, and IL-12, cytokines that induce hormone sensitivity and stimulate cellular immunity, have also been used to treat advanced breast cancer (Swain 1991; Fehniger and others 2002; Hsing and others 2012). Although treatment with IL-2 or IL-6 alone, IL-2 combined with IFN- α , G-CSF or trastuzumab, and IL-12 and trastuzumab is well tolerated (Nicolini and others 2006), they had no clear antitumor effect or have improvement beyond each individual treatment. Clinical outcome was also not improved (Nicolini and Carpi 2008). Treatment with IFNs (IFN- α , IFN- β , and IFN- γ), alone or in combination, had no immunological effects or significantly improved clinical outcomes compared with conventional treatment (Nicolini and Carpi 2008).

TGF- β is a notable target, based on its tumor-supportive function in late-stage tumors. Several approaches for the blocking of TGF- β signaling have been developed, including antibodies. The 1D11 antibody, which blocks all 3 isoforms of TGF- β , inhibits 4T1 growth and metastasis. In contrast, blockade of TGF- β in MDAMB-231 cells, which, unlike 4T1 cells, express low levels of TGF- β , does not affect their growth (Liu and others 2012a). TGF- β blockade normalizes the tumor vasculature, improves chemotherapy delivery into tumors, and decreases angiogenic gene expression, including VEGF and IL-8 (Liu and others 2012a). Further, TGF- β blockade normalizes the interstitial matrix by reducing collagen density, improving the transport of nanoparticles from the perivascular space into deeper areas of the tumor, and enhancing the treatment of breast cancer patients (Liu and others 2012a).

1D11 prevents bone metastasis in animal models, significantly reducing tumor burden in the bone and osteolytic lesion areas. Tumor-bearing mice which have been treated with 1D11 double their bone volume, suggesting that anti-TGF- β can be used to treat bone loss in breast cancer (Biswas and others 2011). Moreover, inhibition of TGF- β signaling in human bone marrow MSCs blocks their differentiation into CAFs, induced by the tumor microenvironment, and the consequent protumor effects, improving the safety of MSC-based therapies in cancer patients (Shangguan and others 2012).

Normalization of abnormal vessels in mammary tumors can also be achieved by blocking vascular endothelial growth factor receptor-2 with DC101, an anti-VEGF-receptor-2, improving the delivery of smaller nanoparticles (diameter, 12 nm) while hindering that of larger nanoparticles (diameter, 125 nm) (Chauhan and others 2012), which can be valuable in directing specific drugs to the tumor.

TGF- β signaling can be blocked with other approaches, such as translational inhibition by antisense oligonucleotides, small-molecule inhibitors, and peptide aptamers to Samd proteins (Kelly and Morris 2010; Zu and others 2012). GC1008 and 2G7 are 2 other high-affinity monoclonal antibodies to TGF- β that can neutralize all 3 isoforms, but they are associated with certain drawbacks, such as side effects, including generalized inflammation, autoimmune reactions, and tumorigenic risk (Kim and others 2001; Cheng and others 2008; Zu and others 2012).

The mAb7E anti-IL-20 also reduces tumor growth, suppresses bone colonization, mitigates osteolysis, and improves bone density in mice that have been injected with breast cancer cells (Hsu and others 2012).

Concluding Remarks

New data on breast cancer immunology from the past several years suggest that many long-established and widely accepted paradigms be revised. We have reviewed data that have led to novel models of the biology and function of breast cancer cells. The cytokines that we have discussed are regulated by molecules which were originally believed to be exclusive to the endocrine system: sex steroids. These findings engendered a new concept of bidirectional communication between the endocrine and immune systems under normal circumstances, not necessarily during disease. Finally, the development of drugs that specifically target cytokines, such as the IL-6/sIL-6R pathway, will be valuable in the treatment of breast cancer, in which immune inflammation has a protagonic function.

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Address correspondence to:
 Dr. Jorge Morales-Montor
 Departamento de Inmunología
 Instituto de Investigaciones Biomédicas
 Universidad Nacional Autónoma de México
 AP 70228
 México City D.F. 04510
 México

E-mail: jmontor66@biomedicas.unam.mx
 jmontor66@hotmail.com

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