Microenvironment and Immunology

S100A7 Enhances Mammary Tumorigenesis through Upregulation of Inflammatory Pathways

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Abstract
S100A7/psoriasin, a member of the epidermal differentiation complex, is widely overexpressed in invasive estrogen receptor (ER)α-negative breast cancers. However, it has not been established whether S100A7 contributes to breast cancer growth or metastasis. Here, we report the consequences of its expression on inflammatory pathways that impact breast cancer growth. Overexpression of human S100A7 or its murine homologue mS100a7a15 enhanced cell proliferation and upregulated various proinflammatory molecules in ERα-negative breast cancer cells. To examine in vivo effects, we generated mice with an inducible form of mS100a7a15 (MMTV-mS100a7a15 mice). Orthotopic implantation of MVT-1 breast tumor cells into the mammary glands of these mice enhanced tumor growth and metastasis. Compared with uninduced transgenic control mice, the mammary glands of mice where mS100a7a15 was induced exhibited increased ductal hyperplasia and expression of molecules involved in proliferation, signaling, tissue remodeling, and macrophage recruitment. Furthermore, tumors and lung tissues obtained from these mice showed further increases in prometastatic gene expression and recruitment of tumor-associated macrophages (TAM). Notably, in vivo depletion of TAM inhibited the effects of mS100a7a15 induction on tumor growth and angiogenesis. Furthermore, introduction of soluble hS100A7 or mS100a7a15 enhanced chemotaxis of macrophages via activation of RAGE receptors.

Introduction
Human S100A7 (hS100A7) is present within the epidermal differentiation complex on 1q21 chromosome (1) and is predominantly expressed in high-grade ductal carcinoma in situ (DCIS; refs. 2–6). In addition, its expression is significantly associated with estrogen receptor (ER)α-negative and nodal metastasis in invasive ductal tumors (2, 4–6). Furthermore, hS100A7 expression is associated with increased angiogenesis (7). hS100A7 has been shown to modulate tumor growth by activating several signaling pathways (5, 8–10).

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tools for preclinical research. Phylogenetic analyses have shown the mouse ancestor mS100a7a15 to be most related to S100A7 and S100A15 among the human paralogs (22, 23). mS100a7a15 has been shown to be upregulated in carcinogen-induced mammary tumorigenesis (22). However, the direct functional role of mS100a7a15 in disease progression is not well characterized. In this study, we have generated a novel transgenic mouse model MMTV-rtTA; tetO-mS100a7a15 (MMTV-mS100a7a15) to study the functional significance of mS100a7a15 in breast tumorigenesis. We have used this model to analyze the role of mS100a7a15 in breast cancer growth/metastasis and have shown that mS100a7a15 may enhance tumorigenesis by inducing proinflammatory molecules and recruiting TAMs.

Materials and Methods

Cell culture and transfection

Human breast carcinoma cell line MDA-MB-231 (American Type Culture Collection) and MVT-1 cells derived from MMTV-c-Myc; MMTV-VEGF bitransgenic mice (provided by Dr. Chodosh) were used as control. The identity of these cell lines was regularly verified on the basis of cell morphology. cDNA of S100A7 (OriGene Technologies) and cDNA of mS100a7a15 were subcloned into pIRES2-EGFP (Invitrogen). Cells were transfected with pIRES2-EGFP-hS100A7 or pIRES2-mS100a7a15 using Lipofectamine 2000 and were used for further experiments.

Chemotaxis

The chemotactic assays were carried out using Transwell chambers (Costar 8 µm pore size; ref. 24). Briefly, phorbol-12-myristate 13-acetate (100 ng/mL) THP1-differentiated macrophages (TDM) or murine macrophage RAW264.7 cells (MMIR) were serum starved. Top chambers were loaded with 150 µL of 1 × 10^6 cells/mL in serum-free medium (SFM) and bottom chambers had 500 μL of SFM containing 50 µg/mL of concentrated supernatant obtained from S100A7- or mS100a7a15-overexpressing or vector-expressing MDA-MB-231 cells. Migrated cells were fixed and documented as described (24).

Western blot analysis

Western blot analysis of lysates was done as described (24).

Microarray analysis

Total RNA was collected from S100A7-overexpressing or vector expressing MDA-MB-231 cells using TRizol reagent (Invitrogen). Microarray analysis was done at the Ohio State University (Columbus, OH) core facility using an Affymetrix Microarray gene U133 chip containing 40,000 human genes. The data were deposited in the GEO Expression Omnibus under accession no. GSE32052 (Supplementary Table S1).

Generation of transgenic mice

TetO-mS100a7a15 mice (26) were cross-bred with MMTV-rtTA mice (provided by Dr. Chodosh) to generate bitransgenic MMTV-mS100a7a15 mice. Transgenic littermates were genotyped by PCR using tetO-mS100a7a15 primers (Supplementary Table S1). Female mice were fed with Dox-chow 1 g/kg (Harlan laboratories) and mice fed with normal diet served as controls. All transgenic mice were kept in animal facility of Ohio State University in compliance with the guidelines and protocols approved by the IACUC.

Whole mount analysis of mammary glands

Right inguinal mammary gland #4 were spread on glass slides, fixed and stained overnight with 0.2% (w/v) carmine (Sigma) and 0.5% (w/v) aluminum sulfate (Sigma) as described (27).

Orthotopic injection assay

A total of 1 × 10^5/100 µL of murine MVT-1 cells were injected into mammary gland (#4) of transgenic mice. Injected mice were either fed with Dox-chow 1 g/kg for 28 days or normal diet (control). Tumors were measured weekly with external calipers, and volume was calculated according to the formula V = 0.52 × a^2 × b, where a is the smallest superficial diameter and b is the largest superficial diameter. Orthotopically injected animals were sacrificed 28 days postinjection and tumors were excised and processed (28).

Depletion of macrophages using clodronate liposomes

Clodronate liposomes (clodrolip) were prepared as described (21). Briefly, clodrolip (1.5 mg/kg) was injected intraperitoneally 6 hours after tumor cell implantation and followed by 0.75 mg/kg treatments every 4 days. Control groups received PBS-liposomes at the same time points. The mice were sacrificed 25 days postinjection and tumors were excised and processed.

FACS analysis

For fluorescence-activated cell-sorting (FACS) analysis, freshly prepared single-cell suspension of tumor-infiltrating cells was incubated with anti-F4/80 PE, anti-Cd11b APC, and anti-CD206 Alexa Flour 488 (29). Receptor for advanced glycation end products (RAGE) expression was analyzed by staining with RAGE antibody (Abcam) followed by Alexa Flour 488 antibody. After staining, the cells were analyzed by FACS Caliber using CellQuest software (BD Biosciences).

Immunohistochemistry

Samples from mammary gland and tumors were dissected, fixed in formalin and embedded in paraffin for sections. Standard immunohistochemical techniques were used according to the manufacturer’s recommendations (Vector Laboratories) using antibodies against K67 (Neomarkers, 1:100), CD31 (Santa Cruz 1:100), Keratin-8 (Troma-1 1:100), mS100a7a15 (custom, 1:250), F4/80 (AbD Serotec, 1:50), arginase1 (Santa Cruz, 1:200), and rabbit anti-mouse inducible nitric oxide synthase (iNOS; Abcam, 1:200) for 60 minutes at room temperature. Vectastain Elite ABC reagents (Vector
Laboratories), using avidin DH-biotinylated horseradish peroxidase H complex with 3,3′-diaminobenzidine (Polysciences) and Mayer’s hematoxylin (Fisher Scientific), were used for detection of the bound antibodies.

**Reverse transcriptase and real-time PCR**

RNA was isolated from cells, mouse mammary gland, and tissues using TRIzol reagent (Invitrogen). Reverse transcriptase PCR (RT-PCR) reaction was carried out using RT-PCR kits (Applied Biosystem). Expression of genes analyzed by quantitative PCR (qPCR) was normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) or 18S rRNA using the 2^(-ΔΔCt) method (30). Primers used for RT-PCR and qPCR are listed in Supplementary Table S1.

**Statistical analysis**

Student t test was used to compare different experimental groups. P < 0.05 was considered to be statistically significant. For all graphs, *, P < 0.05; **, P < 0.01.

**Results**

**hS100A7 and mS100a7a15 overexpression induce proliferation and expression of inflammatory cytokines/chemokines**

hS100A7 has been shown to be highly associated with ERα+ breast cancers. Therefore, we first analyzed the effect of hS100A7 overexpression on proliferation of the ERα+ MDA-MB-231 cell line using 2 different clones, S1 and S2. hS100A7 expression was confirmed by Western blot (Fig. 1A, left). hS100A7 overexpression significantly enhanced growth in both the clones, compared with vector control (V; Fig. 1A, right). To determine the mechanism by which hS100A7 may enhance tumorigenesis, we carried out microarray analysis and found that hS100A7 overexpression induced high levels of proinflammatory cytokines/chemokines CXCL1, CXCL8, IL-1α, IL-11, and CSF2 as compared with control (Fig. 1B). The expression of these hS100A7-induced target proteins was further confirmed using qPCR in 2 different clones, S1 and S2 (Fig. 1C).

Phylogenetic analyses have shown that mS100a7a15 is most related to hS100A7 and hS100A15 (22, 23). mS100a7a15 has also been shown to be associated with inflammation (31). Similar to hS100A7, mS100a7a15 overexpression in 2 different clones of MDA-MB-231 (M1 and M2) enhanced proliferation (Fig. 1D, bottom) and expression of inflammatory molecules CXCL1, CXCL8, IL-1α, IL-11, and CSF2 as compared with vector (Fig. 1E). These results suggest that hS100A7 and mS100a7a15 overexpression enhance growth and upregulate proinflammatory cytokine/chemokine production in breast cancer cells.

**mS100a7a15 induces mammary hyperplasia in bitransgenic mice**

It has been reported that mS100a7a15 is upregulated during carcinogen-induced mammary tumorigenesis (22). However, to the best of our knowledge, there is no transgenic/knockout mouse model available to study the role of mS100a7a15 in breast tumorigenesis. Very recently, K5-tTA; tetO-mS100a7a15 mice were generated for studying the role of mS100a7a15 in psoriasis (26). To determine the role of mS100a7a15 in tumorigenesis, we generated an inducible transgenic mouse model by crossing tetO-mS100a7a15 mice with tetracycline-responsive transactivator protein under the murine mammary tumor virus (MMTV-rtTA) promoter mice. In the presence of doxycycline, rtTA protein changes its conformation and binds to tet operator (tet-O) sequences that result in expression of mS100a7a15 in mammary epithelial cells (Fig. 2A). The mice were genotyped with mS100a7a15 and MMTV-rtTA–specific primers (data not shown). Mammary gland derived from MMTV-mS100a7a15 mice that were subjected to Dox-chow (1 g/kg) for 3 months showed mS100a7a15 expression at mRNA levels (Fig. 2B, left). We also observed enhanced mS100a7a15 expression in these mice by immunohistochemistry (IHC; Fig. 2B, right). We further identified the mS100a7a15-overexpressing cells to be of luminal epithelial origin as these cells also express CK8 (Fig. 2B, right). Further morphologic examination of whole mount virgin mammary gland by carmine (Fig. 2C, top) or hematoxylin and eosin (H&E; Fig. 2C, bottom) staining showed ductal hyperplasia in the doxycycline-induced MMTV-mS100a7a15 mice compared with uninduced mice. These findings indicate that overexpression of mS100a7a15 in mouse mammary gland induces hyperplasia.

**mS100a7a15 overexpression in mammary glands enhances proliferative, inflammatory, and signaling pathways**

We analyzed the expression of phospho-STAT3, phospho-AKT, phospho-ERK, and cyclin D1 in mammary gland as these molecules have been shown to be associated with proinflammatory and proliferative responses and are activated in breast cancer tissue (12, 13, 32). We observed enhanced phosphorylation of STAT3, ERK, and AKT in doxycycline-treated MMTV-mS100a7a15 mice (Fig. 2D). We also observed enhanced expression of cyclin D1 by Western blot (Fig. 2D) and expression of K67 and cyclin D1 by IHC (Fig. 2E) in doxycycline-induced MMTV-mS100a7a15 mice. Because STAT3 has been shown to enhance macrophage infiltration to the tumors (12), we further analyzed the recruitment of macrophages in the mammary gland of these mice. We found an increase in macrophages in doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 2E). MMPs are known to degrade extracellular matrix (ECM) proteins in the cellular microenvironment and significant correlation between TAM count and MMP expression has been observed in tumor (33–35). We observed enhanced MMP2 expression in the mammary gland of doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 2E). These data indicate that mS100a7a15 overexpression induces hyperplasia, activates STAT3/AKT/ERK pathways, and enhances the macrophage recruitment.

**mS100a7a15 enhances tumor growth in an orthotopic syngeneic breast cancer model**

hS100A7 has been shown to increase tumor growth in nude mice (5, 7). We further analyzed the role of mS100a7a15 in tumor progression, by implanting highly aggressive MVT-1 cells (25) into the mammary gland of MMTV-mS100a7a15 mice. Five days prior to injection, mice (n = 5) were fed with...
mS100a7a15 overexpression enhances TAM recruitment in a syngeneic mouse model

TAMs have been shown to be a major component of inflammatory infiltrates seen in tumors (18, 20). Initially, MVT-1–derived primary tumors were evaluated by IHC with macrophage marker F4/80. F4/80+ macrophages were enhanced in tumor tissues of doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 3B). We further analyzed macrophage infiltration in the tumors by flow cytometry. As shown in Fig. 3C, the CD11b+/F4/80+ macrophage infiltration was increased by approximately 42% in doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice. We also analyzed other cell types such as Gr-1, T, and B cells but did not notice any significant increase in the doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (data not shown).
TAMs can be divided into 2 main classes, tumor-suppressive M1 (classically activated) and tumor-promoting M2 (alternative). M1 macrophages are characterized among other factors by expression of iNOS whereas M2 macrophages have a decreased level of iNOS and are identified by their signature expression of arginase-1 (Arg-1) and mannose receptor (CD206; ref. 36). An increase of 29% CD11b+CD206 (M2 TAM) was observed in tumors derived from doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 3D). We further confirmed increased M2 phenotype by IHC for enhanced expression of Arg-1 and decreased iNOS expression (Fig. 3E, left). Changes in expression of Arg-1 or iNOS genes were also detected by qPCR (Fig. 3E, right). These results suggest that mS100a7a15 may enhance tumor growth by recruiting M2 macrophages to the tumor site.

**mS100a7a15 overexpression induces the expression of metastatic and angiogenic markers**

We examined the expression of prometastatic and angiogenic genes, such as CCL2, COX2, MMP9, and VEGF, in the MVT-1–derived tumors. These genes were significantly upregulated in doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 4A and B). We also observed an approximately 2.7-fold increase in CD31+ blood vessels as detected by IHC in doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 4C and D). These studies suggest that mS100a7a15...
may enhance expression of metastatic and angiogenic markers.

**mS100a7a15 overexpression enhances metastasis in orthotopic breast cancer models**

We further investigated the role of mS100a7a15 on spontaneous metastasis in MMTV-mS100a7a15 mice injected with MVT-1 cells. We observed a significant increase in surface lung metastases in the mice treated with doxycycline compared with untreated mice (*P* < 0.049; Fig. 5A and B). Because TAMs have been shown to enhance metastasis (17, 18, 20), we further analyzed the infiltrations of macrophages in the lung tissues and observed enhanced expression of F4/80+ macrophages (Fig. 5C) and Arg-1 expression but decreased iNOS expression (Fig. 5C) in doxycycline-induced MMTV-mS100a7a15 compared with untreated mice. We also observed a significant increase in prometastatic genes, such as *CCL2* and *VEGF*, in the metastatic lung tissue of doxycycline-induced MMTV-mS100a7a15 compared with uninduced mice (Fig. 5D). These studies suggest that mS100a7a15 may enhance metastasis through enhancement of prometastatic genes in the metastatic lungs.

**Macrophage depletion inhibits tumor growth and angiogenesis**

To specifically analyze the role of mS100a7a15 overexpression in TAM recruitment, we selectively inhibited macrophages using clodrolip (liposome-encapsulated clodronate) as previously described (21). Clodrolip treatment significantly reduced tumor growth in MVT-1–derived doxycycline-induced MMTV-mS100a7a15 compared with control liposome–treated mice (Fig. 6A and B). Quantification of the number of F4/80+ TAMs and CD206+ M2 TAMs by FACS (Fig. 6C) and IHC (Fig. 6D and E left) revealed a significant decrease in TAMs and M2 TAMs in clodrolip treated compared with control liposome–treated mice fed with doxycycline diet. We also observed significant reduction in angiogenesis as detected by CD31 immunohistochemical staining in clodrolip-treated MMTV-
mS100a7a15 compared with control liposome–treated mice fed with doxycycline diet (Fig. 6D, bottom, and 6E, right). These studies further confirm that mS100a7a15 may enhance tumorogenesis and angiogenesis through recruitment of macrophages.

**Soluble hS100A7 and mS100a7a15 enhance chemotaxis in macrophages in vitro**

Previously, soluble hS100A7 and mS100a7a15 were shown to induce chemotaxis in leukocytes by binding to RAGE (26, 37). However, not much is known about the role of these proteins in regulating monocyte/macrophage chemotaxis. We analyzed the effect of hS100A7 secreted into the conditioned media on chemotaxis of the differentiated monocytic cell line THP-1. hS100A7 expression was observed in the supernatant of hS100A7-overexpressing MDA-MB-231 cells (Fig. 7A, left). We also observed expression of RAGE in TDM (Fig. 7A, right). Furthermore, we observed a significant increase in the chemotaxis of TDM upon stimulation with conditioned media of hS100A7-MDA-MB-231 cells. These effects were significantly abrogated by blocking RAGE (Fig. 7B). We have also shown that RAGE is expressed on the surface of MMR (Fig. 7C). We also observed mS100a7a15 expression in the conditioned media of mS100a7a15-overexpressing MDA-MB-231 cells (Fig. 7C, right). In addition, conditioned media of mS100a7a15-overexpressing MDA-MB-231 cells enhanced migration of MMR and these effects were blocked by murine RAGE–neutralizing antibodies (Fig. 7D). These studies suggest that hS100A7/mS100a7a15 may enhance monocyte/macrophage chemotaxis through RAGE.

Discussion

hS100A7 has been shown to be associated with the ER+ phenotype and is predominantly expressed in high-grade DCIS. Furthermore, expression of hS100A7 in breast tumors represents a poor prognostic marker and correlates with lymphocyte infiltration and high-grade morphology (2, 6, 7). Although a number of putative functions have been proposed for hS100A7, its biologic role particularly in breast cancer remains to be defined.

In this study, we characterized the tumor-enhancing effects of hS100A7 and mS100a7a15 in MDA-MB-231 breast cancer cells and inducible MMTV-mS100a7a15 mouse model systems. We observed enhanced proliferation and production of proinflammatory molecules IL-1α, IL-11, CSF2, CXCL1, and CXCL8 in hS100A7 and mS100a7a15-overexpressing cells compared with vector control. These molecules have been shown to play a major role in tumor progression and invasion (38, 39).

In an inducible transgenic mouse model system, we observed a significant increase in the number of primary ducts and side branches in mice expressing mS100a7a15 in mammary epithelial cells. This increase in mammary ductal epithelial hyperplasia was caused by enhanced proliferation as indicated by increased expression of Ki67 and cyclin D1 in the ductal epithelial cells of induced mice. We observed increased expression of STAT3 and MMP2 in mammary gland of inducible mice. Overexpression of cyclin D1 has been reported in up to 50% of primary breast tumors (40). In addition, STAT3 has been shown to be constitutively activated in 35% to 60% of breast cancers (12).

We also showed that mS100a7a15 overexpression significantly increased tumor growth in the syngeneic orthotopic model. Further elucidation of mechanisms revealed that mS100a7a15 may enhance growth and metastasis through recruitment of M2 TAMs. M2-polarized TAMs are known to drive tumor progression by stimulating angiogenesis and metastasis (17, 18, 20). We have shown that M2-specific markers are increased whereas expression of M1 markers is...
decreased in MVT-1–derived tumors and lung tissues of doxycycline-induced mS100a7a15 mice. We further determined whether selective depletion of macrophages would inhibit tumor growth. It has been shown previously that macrophages may be selectively depleted in mice using clodrolip (21). Therefore, we treated MVT-1 tumor–bearing mice with intra-peritoneal inoculations of clodrolip or with an empty liposome control at various points throughout tumor progression. We observed approximately 80% depletion of macrophage content of the tumors compared with control liposome–treated tumors in doxycycline-induced MMTV-S100a7a15 mice. We observed that clodrolip-mediated reduction of TAMs also caused dramatic reduction in tumor growth in doxycycline-induced MMTV-mS100a7a15 mice. These results suggest that mS100a7a15 may enhance tumor growth through enhancing recruitment of macrophages to the tumors. Previous studies have reported that an intimate relationship between macrophages and tumor cells is required for tumor growth and metastasis (18, 41). We have shown that hS100A7 and mS100a7a15 enhanced chemotaxis of monocyte/macrophages through RAGE. RAGE expression has been detected in a variety of human tumors including breast (42). It has been shown that the blockade of RAGE in glioma-suppressed tumor growth (43).

Although mS100a7a15 has been shown to enhance CD4-positive T-cell populations in mS100a7a15-overexpressing keratinocytes from psoriasis mouse model (26), we did not observe a significant change in CD4-positive T cells as detected by FACS in tumors derived from our MVT-1 orthotopic syngeneic model. This difference may be attributed to the different model systems used in each study. Another possibility is that the recruitment of macrophages could result from enhanced production of chemokine CCL2 in tumors from doxycycline-induced MMTV-mS100a7a15 mice. CCL2 has been shown to recruit inflammatory monocytes/macrophages that in turn stimulate breast tumor growth and metastasis (44). In breast cancer, macrophage infiltration and CCL2 expression have been correlated with metastatic disease and poor prognosis (45–47). We also observed significant increase in spontaneous metastasis and M2 TAMs in orthotopic syngeneic MMTV-mS100a7a15 mouse model. Previous studies have shown that TAMs promote metastasis by enhancing prometastatic and proangiogenic activities within the tumor microenvironment (17, 18, 20). We have shown enhanced expression of prometastatic and proangiogenic molecules such as CCL2 and VEGF in metastatic lung tissues. Also, we observed enhanced gene expression of CCL2, VEGF, COX2, and MMP9 in primary tumors.
These molecules have been shown to enhance metastasis of various cancers (33, 44, 48–50). Previously, it has been shown that hS100A7 modulates VEGF expression in MDA-MB-468 cells (7). These studies suggest hS100A7, which has been shown to be associated with highly invasive breast cancer subtypes (31), may enhance metastasis through enhancement of pro-metastatic and angiogenic molecules.

In summary, using novel mS100a7a15 transgenic and orthotopic syngeneic mouse models, we have shown that mS100a7a15 overexpression in mammary epithelial cells enhances hyperplasia, tumor growth, angiogenesis, and metastasis. As shown in model (Supplementary Fig. S1), our studies for the first time revealed that hS100A7/mS100a7a15 produced by epithelial cells may enhance proliferation and recruit TAMs to tumor site by endocrine mechanism through RAGE activation. Recruitment of TAMs into tumor microenvironment may in turn stimulate tumor growth and metastasis by enhancing expression of prometastatic and proinflammatory molecules such as CCL2, COX2, MMP9, and VEGF. Thus, these studies suggest that S100A7 may enhance tumor growth and metastasis especially in ERα+ tumors through a novel mechanism by activating proinflammatory and metastatic pathways.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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