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Fibrillar Human Serum Albumin Suppresses Breast Cancer Cell Growth and Metastasis

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1. Introduction

1.1 Breast cancer classification

Breast cancer is one of the most common cancers among women worldwide and approximately one-third of women diagnosed will eventually develop metastases and die (Jemal et al, 2010). Breast cancer is heterogeneous at the molecular, histopathologic and clinical levels and is commonly classified into several categories according to multiple schemes, each based on different criteria. A typical description of breast cancer can be comprised of tumor grade, histologic type, tumor stage, and the expression of proteins and genes etc. (McSherry et al, 2007). Normal non-cancerous cells are differentiated and have specific cell shapes and functions; whereas, cancer cells lose differentiation (de-differentiate), have less uniform nuclei, and exhibit uncontrolled cell division. Pathologists, therefore, determine breast cancer by grade according to the degree of differentiation of cells compared to normal breast cells: highly differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade). Cancers classified as high grade generally have a worse prognosis (McSherry et al, 2007). The majority of breast cancers are derived from the epithelium lining the ducts or lobules of the breast. They can be classified histologically according to characteristics seen upon light microscopy of biopsy specimens. Histologic classification is divided into: ductal carcinoma in situ (DCIS), invasive ductal carcinoma, and invasive lobular carcinoma (McSherry et al, 2007). Breast cancer can further be classified using the TMN Classification of Malignant Tumors, TMN stage is based on tumor size, lymph node micrometastasis, and macrometastasis, where 'T' describes tumor size; 'N' indicates whether or not the tumor has spread to the lymph nodes; and 'M' indicates whether or not distant metastasis has occurred. Larger tumor size with lymph nodal spread and distal metastasis has a worse prognosis (Gonzalez-Angulo et al, 2007). Expression of certain proteins and genes can also be used to classify breast cancer (McGrogan et al, 2008; Stickeler et al, 2009). Whole-genome analysis using expression microarray and immunohistochemical analysis has revolutionized the understanding of breast carcinomas in recent years, and led to the discovery of five distinct subtypes of breast carcinomas (luminal A, luminal B, HER-2 overexpression, basal-like, and normal-like), each with unique recognizable phenotypes and clinical outcomes (McGrogan et al, 2008; Stickeler et al, 2009). By using classification to characterize each cancer patient, it may help select the suitable treatment strategies to achieve an optimal outcome and increase therapeutic efficacy.

2. Breast cancer metastasis

In the United States, about 178,480 new cases of invasive breast cancer were diagnosed in 2007 and approximately 40,460 women died (Jemal et al, 2007). In 2010, about 207,090 new breast cancer cases were diagnosed and 39,840 died (Jemal et al, 2010). The breast cancer incidence rate has been decreasing in the USA since 1999 and the majority of 40,000 women died each year were due to breast cancer metastasis (Giordano & Hortobagyi, 2003; Jemal et al, 2010). Cancer metastasis is a complex process that includes intercellular and intracellular signaling, activation, adhesion, migration and invasion (Im et al, 2004; Lee et al, 2006). Epithelial-to-mesenchymal transition (EMT) is also thought to be involved in cancer metastasis. EMT may promote cancer-cell progression and invasion into the surrounding microenvironment. Historically, epithelial and mesenchymal cells are distinct in their unique cellular appearance and the morphology of the multicellular structures they create (Shook & Keller, 2003). A typical morphology of epithelium is sheeted and thick with individual epithelial cells abutting each other in a uniform array. Cell-to-cell junctions and adhesions between neighboring epithelial cells hold cells tightly together and inhibit the movement of individual cells away from the epithelial monolayer. Mesenchymal cells, on the other hand, possess usually a more extended and elongated shape and do not exhibit either a regimented structure or tight intracellular adhesion. Mesenchymal cells are irregular in shape and not uniform in composition or density. Adhesions between mesenchymal cells are not as strong as those of their epithelial counterparts, allowing for increased migratory capacity. The transformation of an epithelial cell into a mesenchymal cell not only alters cellular morphology, architecture, adhesion capacity, and migration capacity but also enhances capability of the cell to metastasize (Shook & Keller, 2003). Conversely, the transformation of a mesenchymal cell into an epithelial cell (MET) may prevent cell invasion and suppress cell metastatic ability.

3. Breast cancer therapy

To date, adjuvant and neo-adjuvant therapies are commonly used in cancer metastasis therapy (McGrogan et al, 2008). Currently, there are three main groups of medications used for adjuvant breast cancer treatment: (1) hormone blocking therapy; (2) chemotherapy; and (3) monoclonal antibody therapy (McGrogan et al, 2008). The cell surfaces of some breast cancers are estrogen receptors positive (ER⁺) and/or progesterone receptors positive (PR⁺) and the cells require estrogen to continue growing. These cancers can be treated with drugs that block either the hormone receptors, such as tamoxifen or the production of estrogen, such as anastrozole (Arimidex) or letrozole (Femara). The drugs that inhibit estrogen production are only suitable for post-menopausal patients (Gonzalez-Angulo et al, 2007). Combination chemotherapy is predominately used for patients at stages 2-4, being particularly beneficial in ER-breast cancer. One of the most common treatments is cyclophosphamide plus doxorubicin (Adriamycin) which destroys rapidly growing or replicating cancer cells by causing DNA damage; however, these drugs also damage normal cells causing serious adverse effects. Damage to heart muscle is the most dangerous complication associated with doxorubicin. Taxane drugs such as paclitaxel, a microtubule-stabilizing agent that interferes with spindle microtubule dynamics causing cell-cycle arrest and apoptosis through interaction with β -tubulin (Bergstralh & Ting, 2006), is also used in the breast cancer metastasis therapy. However, resistance to paclitaxel is common and there

is a need to identify patients most likely to respond to treatment (McGrogan et al, 2008). Other treatments like methotrexate and fluorouracil are also used in chemotherapy. Approximately 15-20% of breast cancers have an amplification of the HER-2/neu gene or overexpression of its protein product. This receptor is a marker for poor prognosis that is associated with increased disease recurrence during the period of cancer therapy (Brown et al, 2008). Trastuzumab (Herceptin), a humanized monoclonal antibody that specifically binds to the extracellular domain of the HER-2 receptor, has improved the 5-year disease free survival of stage 1-3 HER-2⁺ breast cancers to about 87%. However, about 2% of patients suffer significant heart damage after Herceptin treatment (Brown et al, 2008). Trastuzumab has also been used in combination with doxorubicin and proven to be highly effective for metastatic breast cancer patients with HER-2 over-expressing tumors. However, this regimen causes severe cardiac toxicity in 27% of treated patients when the two substances are given concurrently (Stickeler et al, 2009). Lapatinib (Tykerb, GlaxoSmithKline) is an orally active small molecule that inhibits the tyrosine kinases of HER-2 and epidermal growth factor receptor type 1 (EGFR). In preclinical studies, lapatinib showed no cross-resistance with trastuzumab (Jahanzeb, 2008).

Conventional radiotherapy is usually given after surgery to destroy remaining tumor cells that may have escaped surgery. Recently, radiotherapy has also been given at the time of surgery and found to reduce the risk of recurrence by 50-66% (Belletti et al, 2008). Despite such improvements in treatment modalities, there is still a high rate of failure among adjuvant interventions mainly due to tumor invasion and metastasis. Therefore, the search for new therapeutic targets and the development of new inhibitors of tumor cell resettlement and metastatic growth continues.

4. Surface membrane integrins as potential drug-discovery targets

It is well known that cell activation, migration, proliferation, and differentiation require direct contact between cells and the extracellular matrix (ECM). Cell-to-cell and cell-to-matrix interactions are mediated by the integrin, selectin, cadherin and/or immunoglobulin families and several studies have focused on investigating cancer therapies based on the integrin superfamily. Integrin expression on cancer cells is frequently associated with cancer progression and metastasis; therefore, targeting small-molecule antagonists of the integrin superfamily provides an opportunity to suppress cancer development and metastasis (Mullamitha et al, 2007). $\beta 1$ integrin, which frequently aberrantly expressed in human breast carcinomas, has been verified to play a central role in metastasis and contribute to growth factor receptor signaling. Inhibition of the $\beta 1$ integrin signaling pathway has been shown to abolish the formation of metastasis in breast and gastric cancer models. Additionally, the $\beta 1$ integrin signaling pathway also plays a significant role in mediating resistance to cytotoxic chemotherapies by enhancing cell survival in hematologic malignancies, lung, and breast cancers (Lu et al, 2008). Recent studies have shown that $\alpha 1\beta 1$, $\alpha 2\beta 1$, and $\alpha 3\beta 1$ integrins regulate hepatocarcinoma cell invasion, angiogenesis of human squamous cell carcinoma, and increase migration and invasion of malignant glioma, melanoma and mammary adenocarcinoma cells, respectively. Expression of $\alpha 5\beta 1$ integrin in colon cancer cells decreases HER-2-mediated proliferation (Kuwada et al, 2005). Loss of the $\alpha 7\beta 1$ integrin in melanoma increases highly tumorigenic and metastatic phenotypes (Ziober et al, 1999). Several preclinical and clinical trials have shown that some integrin targeting antibodies can effectively block tumor growth and metastasis. These antibodies include MEDI-522 (vitaxin)

against $\alpha\beta3$ integrin (Brooks et al, 1994), CNTO 95 against both $\alpha\beta3$ and $\alpha\beta5$ integrins (Mullamitha et al, 2007), 17E6 against $\alpha\beta3$, $\alpha\beta5$, and $\alpha\beta1$ integrins (Mitjans et al, 2000), LM609 against $\alpha\beta3$ integrin, and Tysabri (natalizumab) against $\alpha4$ integrins (O'Connor, 2007). In addition, $\beta1$ integrins possess a RGD-binding region, therefore, based mainly on their RGD containing peptides and RGD peptidomimetics, some small molecule integrin antagonists have also shown potent inhibition of angiogenesis (Kumar et al, 2001). Both fibronectin and its receptor integrin $\alpha5\beta1$ directly regulate angiogenesis (Kim et al., 2000). Thus, antagonist(s) of $\alpha5\beta1$ integrin might be useful targets for the inhibition of angiogenesis associated with human tumor growth, and neovascular-related ocular and inflammatory diseases (Pasterkamp et al, 2003; Suzuki et al, 2007). Further, our own studies recently found that fibrillar bovine serum albumin (F-BSA) induced apoptosis in human breast duct carcinoma cell line T47D, and fibrillar fibronectin (F-FN) induced apoptosis in human breast cancer cell line MCF-7. F-BSA and F-FN induced BHK-21 cell (baby hamster kidney cell) apoptosis through negatively regulating the integrin/FAK/Akt/GSK-3 β signaling pathway and activating SHP-2 and RhoA/ROCK (Huang et al, 2009; Huang et al, 2010). Together these results suggest that inhibition of the $\beta1$ integrin signaling pathway may provide a promising therapeutic approach to breast cancer metastasis.

5. Formation and purification of fibrillar human serum albumin

Some diseases like Alzheimer's disease, transmissible spongiform encephalopathies, pancreatic islet amyloidosis, and familial amyloidosis are caused primarily by amyloid-like fibrils aggregation in organs and in the circulation (Jackson & Clarke, 2000). Recently, it has been documented that amyloid-like fibrils are cytotoxic to neuronal cells, BHK-21 cells, SKOV-3, and MCF-7 cancer cells (Gharibyan et al, 2007; Su & Chang, 2001; Zamotin et al, 2006). Whether the fibrillar proteins may be used as anti-cancer drugs in the cancer therapies is largely unclear. We have developed a novel process to convert globular proteins, bovine serum albumin and fibronectin, to fibrillar forms using detergent assisted refolding chromatography (Huang et al, 2009; Huang et al, 2010). This procedure is easier to perform than other methods reported to convert proteins to fibrillar structures such as glycation, sonication, or high temperature incubation (Azakami et al, 2005; Taboada et al, 2006). Fibrillar protein F-BSA induced apoptosis in human breast duct carcinoma cell line T47D, and F-FN induced apoptosis in human breast cancer cell line MCF-7 suggesting that fibrillar proteins may have therapeutic effect in human breast cancer cells. We thus further investigated the effects of the fibrillar form of human serum albumin (F-HSA) on the malignant breast cancer cell lines, TS/A and MDA-MB-231. We chose F-HSA for further study for two reasons: first, because F-HSA is less likely to provoke an immune response in the human body; and second, because HSA is easier to obtain and less costly than FN. We produced F-HSA using the same process as was used to produce F-BSA. In brief, 20 mg of HSA from human serum was dissolved in 10 ml of PBS with 1% SDS (w/v). The HSA solution was sonicated for 5 minutes and subsequently applied to a Superdex-200 column previously equilibrated with the eluting buffer (25 mM Tris-HCl, pH 8.0, 1 mM EDTA, 0.1 M NaCl, and 0.05% SDS). The fractions that contained HSA were pooled and dialysed against PBS to remove SDS. The yield of the F-HSA was about 67% (Fig. 1). The F-HSA produced was then tested for fibrillar structure by transmission electron microscopy (TEM). For TEM analysis of F-HSA, 2 mg/ml of protein was applied to a 300-mesh carbon-coated copper

grid. Excess samples were removed, and the grid was air dried. The protein-bearing grid was negatively stained with 1% (w/v) phosphotungstic acid for 1 minute. Transmission electron micrographs were observed at 20,000–150,000 \times magnification at 75 kV on a Hitachi H-7000 electron microscope. TEM analysis showed that F-HSA did indeed have a fibril structure (Fig. 2).

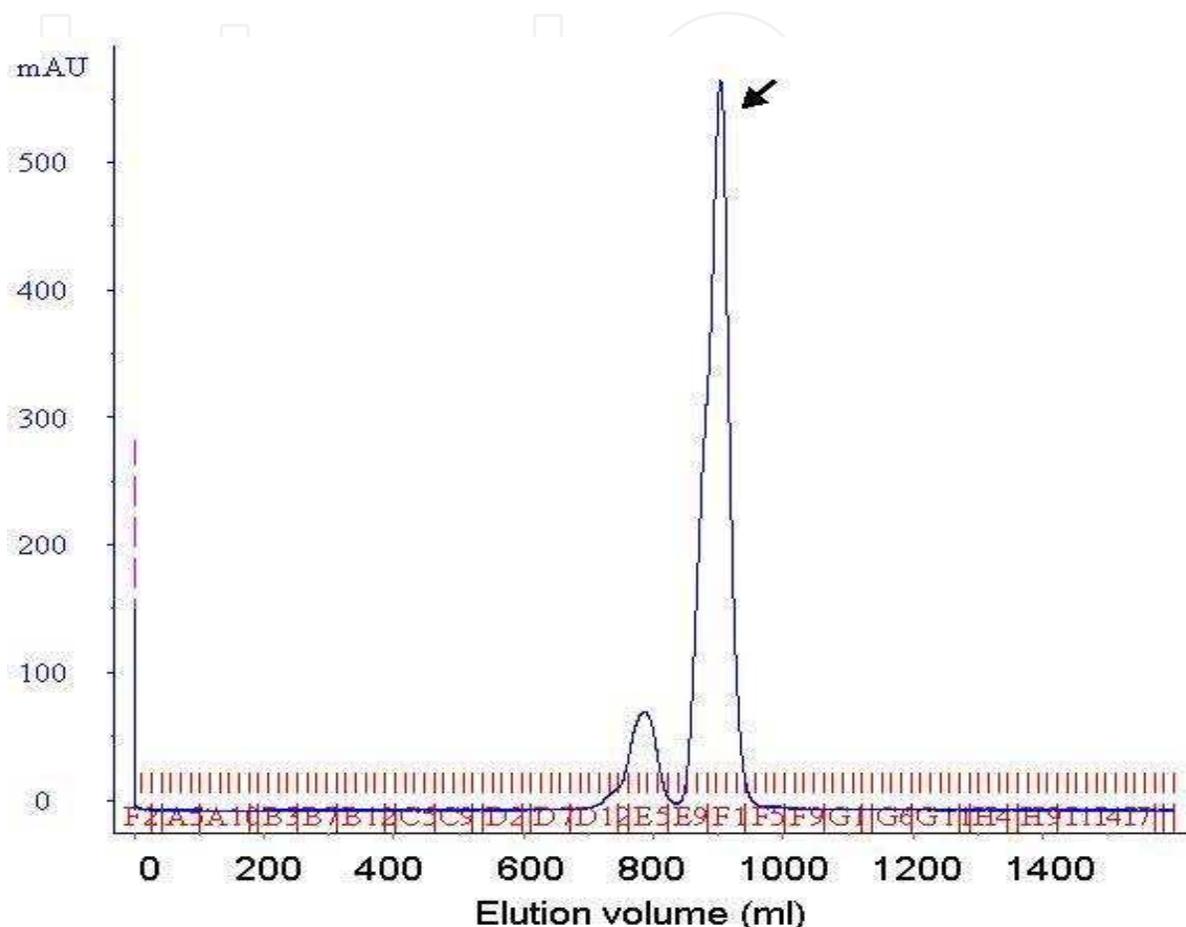


Fig. 1. Elution profile of F-HSA from a Superdex-200 column. HSA (2 mg/ml dissolved in PBS containing 1% SDS) was applied to a Superdex-200 column and eluted at a rate of 1 ml/min with a buffer solution containing 0.05% SDS. Arrow shows F-HSA.

Specific binding to Thioflavin T (ThT) is one of the characteristics of amyloid-like proteins. ThT fluorescence assay was, thus, used to identify amyloid-like fibrils (LeVine, 1999). Like A β (1-42), which is known to have fibrillar structure and was used as a positive control, F-HSA obtained from the Superdex-200 column exhibited a gradual dose-dependent increase in ThT fluorescence level (Fig. 3).

6. Effects of F-HSA on cell viability

Previously, we demonstrated that F-BSA and F-FN induced apoptosis in the less malignant T47D and MCF-7 breast cancer cell lines, respectively (Huang et al, 2009; Huang et al, 2010). In this study, we examine whether F-HSA induced cytotoxicity in the more malignant breast

cancer cell lines, TS/A and MDA-MB-231, using a 3-(4,5-cimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT)-colorimetry assay to measure the cell viability (MERCK, Darmstadt, Germany). TS/A, a murine mammary adenocarcinoma cell line that is estrogen dependent, was cultured in Dulbecco's modified Eagle's medium (DMEM; GIBCO®); and MDA-MB-231 (ATCC **HTB-26**TM), a metastatic human breast cancer cell line that is estrogen independent, was cultured in DMEM/F12 medium (GIBCO®). In brief, 2×10^4 breast cancer cells were incubated in serum-free medium and treated with serial dilutions of F-HSA. After incubation for 24 hours to allow the drug to take effect, 10 μ l MTT solution was added to each well. After incubation at 37°C in 5% CO₂ for another 2 hours to allow the MTT solution to be metabolized, formazan (MTT metabolic product) was resuspended in 200 μ l DMSO. Finally, the proportions of surviving cells were determined by optical density (570 nm test wavelength, 630 nm reference wavelength). The percentage of surviving cells was calculated as $(O.D.\text{treatment}/O.D.\text{control}) \times 100\%$, and the percentage of growth inhibition was calculated as $[1 - (O.D.\text{treatment}/O.D.\text{control})] \times 100\%$. IC₅₀ value is the concentration at which the reagent produces 50% inhibition of cellular viability. F-HSA inhibited growth of the breast cancer cell lines TS/A and MDA-MB-231 in a dose dependent manner with IC₅₀ values of 0.15 and 0.48 μ M, respectively (Fig. 4). F-HSA at concentrations over 0.4 μ M induced dose-dependent cytotoxicity in both TS/A cells and MDA-MB-231 cells, whereas concentrations of 0.1-0.2 μ M did not affect cell viability significantly.

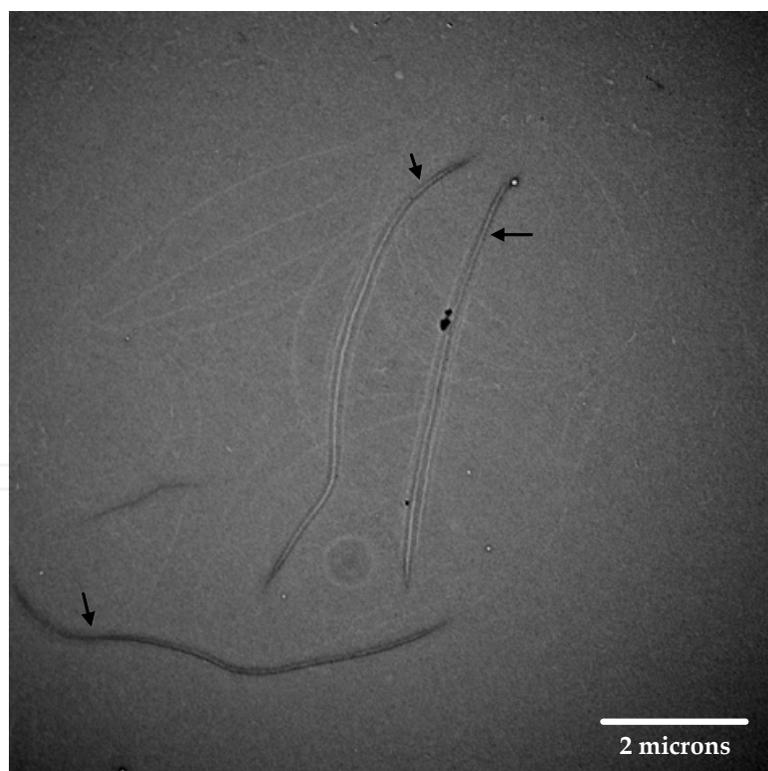


Fig. 2. Ultra-structures of F-HSA were observed by TEM. F-HSA was applied to a 300-mesh carbon-coated copper grid then the grid was air-dried. The F-HSA-bearing grid was negatively stained with 1% (w/v) phosphotungstic acid. Finally, transmission electron micrographs were observed at 20,000–150,000 \times magnification at 75 kV on a Hitachi H-7000 electron microscope. Arrows show F-HSA.

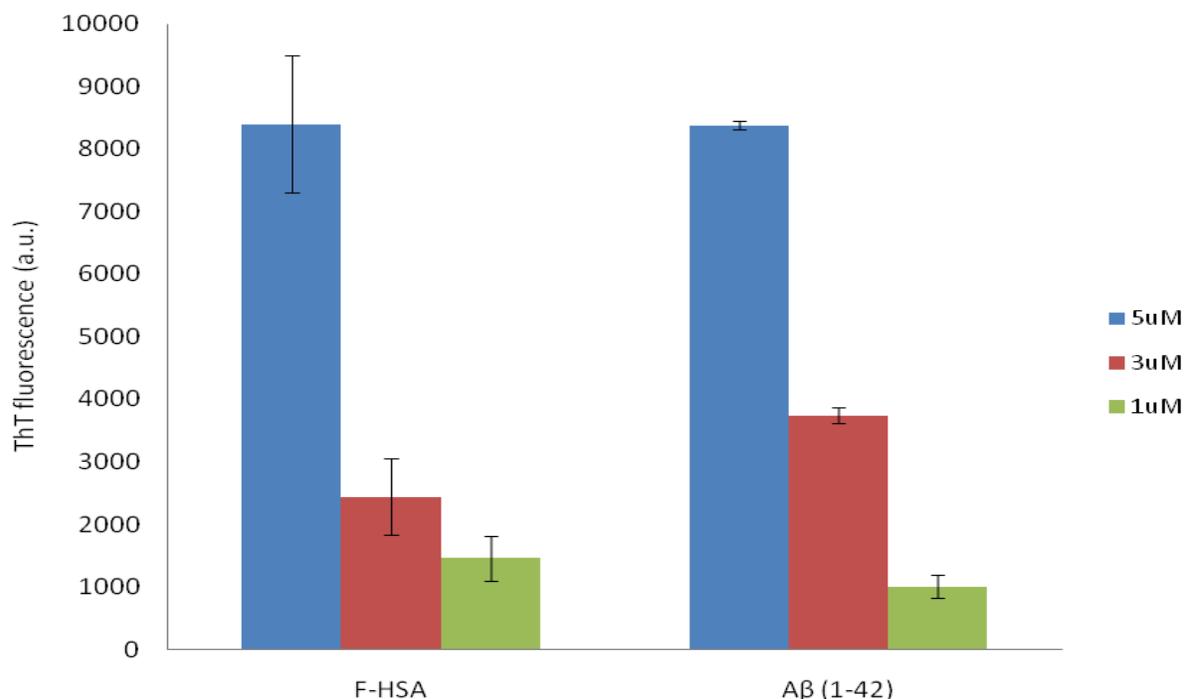


Fig. 3. ThT fluorescence assay of F-HSA. For fluorescence measurements, increasing concentrations of proteins were incubated with 20 μM ThT for 1 h at room temperature, and fluorescence was measured in triplicate on a Wallac Victor² 1420 Multilabel Counter (Perkin Elmer Life Science, Waltham, MA, USA). Excitation and emission wavelengths were 430 nm and 486 nm, respectively. ThT background signal from buffer solution was subtracted from the corresponding measurements. A β (1-42) was used as a positive control.

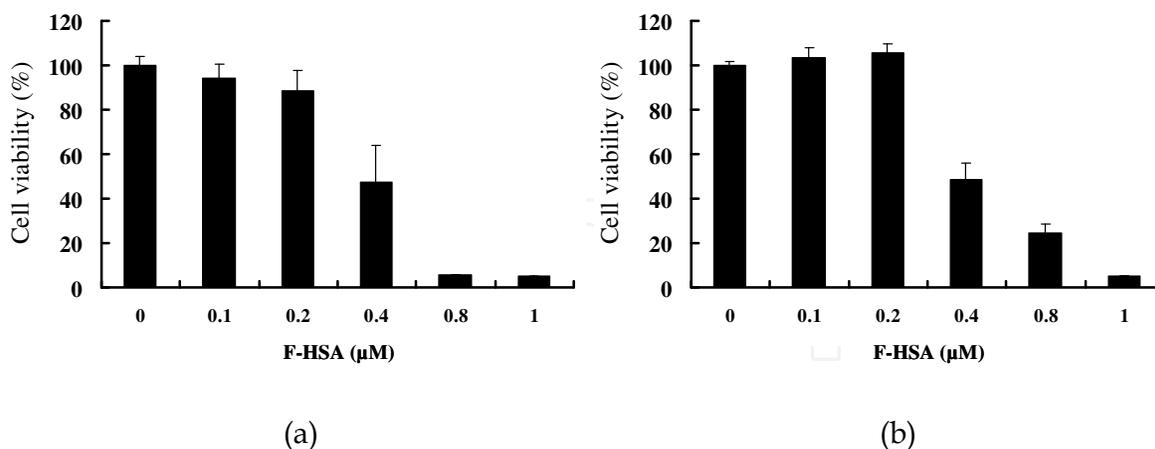


Fig. 4. Effect of F-HSA on viability of TS/A (A) and MDA-MB-231 cells (B).

To understand the effects of F-HSA on cell morphology and MET in TS/A cells and MDA-MB-231 cells, breast cancer cells were treated low concentrations of F-HSA and cell morphology was observed under light microscopy. F-HSA induced a morphological alteration in cells, from a fibroblast-like shape to a round shape (Fig. 5). We also examined whether F-HSA suppressed breast cancer-cell migration at non-cytotoxic concentrations by

wound-healing assay. TS/A and MDA-MB-231 cells were plated onto six-well tissue culture dishes in complete tissue culture medium until they formed a confluent monolayer. The cell monolayer was scratched with a sterile pipette tip to generate a wound (width 2 mm). The remaining cells were washed three times with culture medium to remove cell debris. The medium was immediately replaced with serum-free medium with 0.1 or 0.2 μM of F-HSA, and cultured at 37°C for 24 hours. Spontaneous cellular migration was then monitored at 0 hours (immediately after wounding) and 24 hours (the end of F-HSA treatment) using an inverted microscope (Axiovert 200M; Zeiss) at 100 \times original magnification. The extent of wound healing was determined by the distance (migrating distance) traversed by cells migrating into the denuded area. F-HSA at concentrations of 0.1 to 0.2 μM suppressed cell migration of both TS/A and MDA-MB-231 cells (Figs. 6-7).

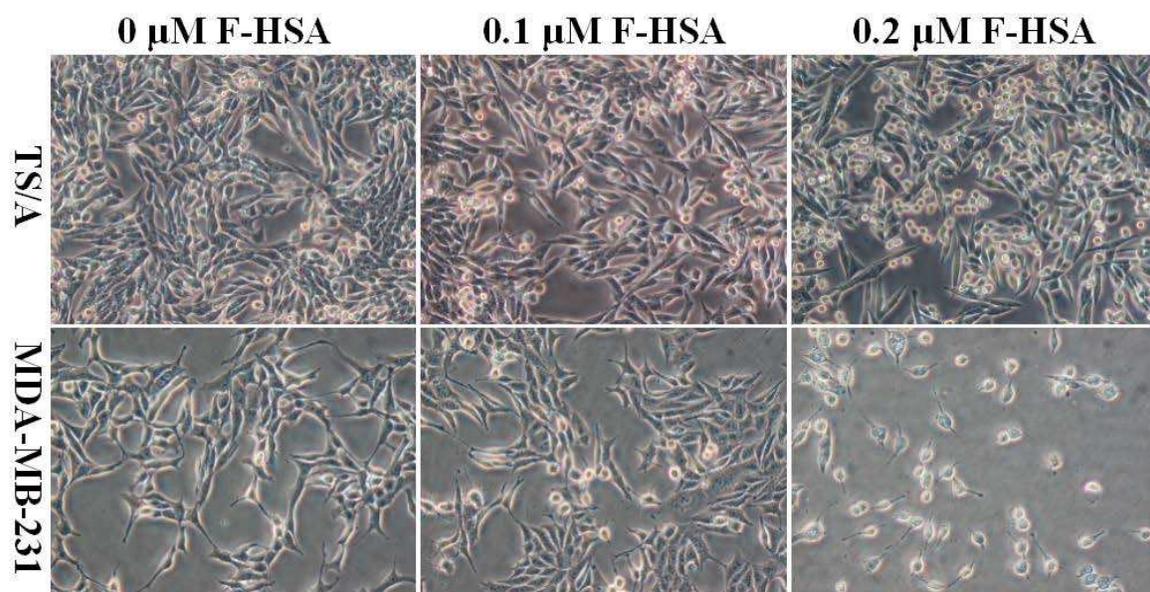


Fig. 5. F-HSA induced morphological alterations and mesenchymal-to-epithelial transition in breast cancer cells. After 0.1 μM and 0.2 μM of F-HSA treatment at 37°C for 24 h, cell morphology was observed under light microscopy. Scale bar, 5 μm

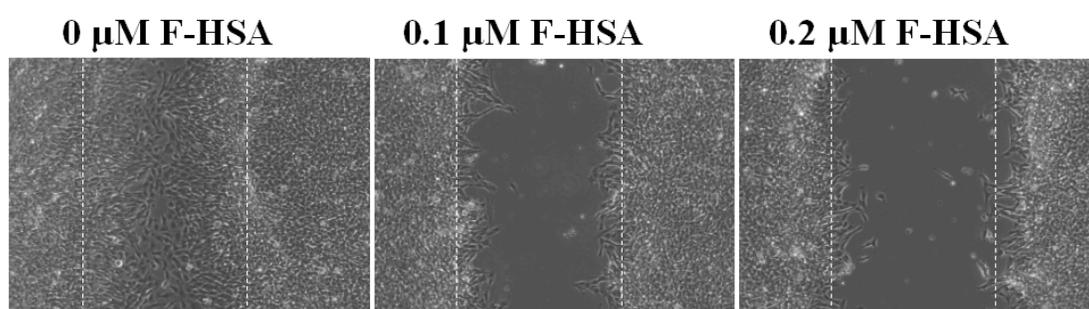


Fig. 6. F-HSA suppressed TS/A cell migration in a breast cancer cell wound-healing assay. After 0.1 μM and 0.2 μM of F-HSA treatment at 37°C for 24 h, cell migration was observed under light microscopy.

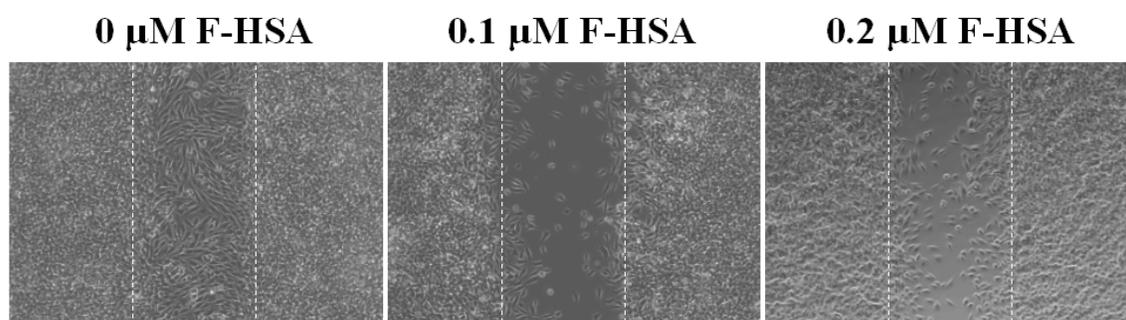


Fig. 7. F-HSA suppressed MDA-MB-231 cell migration in a wound-healing assay. After 0.1 μM and 0.2 μM of F-HSA treatment at 37°C for 24 h, cell migration was observed under light microscopy.

7. F-HSA suppresses breast cancer cell migration via $\beta 1$ integrin signaling pathway

Cell surface receptors mediate cell-to-matrix and cell-to-cell interactions. Integrins are a large family of heterodimeric transmembrane receptors that mediate cell-ECM interactions. In eukaryotic cells, integrins consist of 18 α subunits and 8 β subunits that form 24 different $\alpha\beta$ integrins. The particular combination of α and β subunits in integrin dimers determines their specificity for ligands, which include most of the ECM proteins such as FN and collagen (Plow et al, 2000). Upon activation by ECM proteins, integrins mediate cellular adhesion, migration, survival, and proliferation (Ginsberg et al, 2005). Integrin signaling is activated by ECM proteins or growth factors through focal adhesion kinase (FAK), PI3K, and Akt, a major downstream target of PI3K signaling, known to be involved in various cellular processes such as cell survival, cell cycle, metabolism, protein synthesis, and transcriptional regulation (Mitra & Schlaepfer, 2006). We showed that fibrillar proteins induced cellular apoptosis (Huang et al, 2009; Huang et al, 2010). The mechanism of the cytotoxic effects of F-BSA in BHK-21 cells (baby hamster kidney cell) was due to modulation of the $\alpha 5\beta 1$ integrin/FAK/Akt/GSK-3 β /caspase-3 signaling pathway. Furthermore, F-FN induced cytotoxicity via activating SHP-2 and RhoA/ROCK, and deactivation of Akt/GSK-3 β . Taken together these findings suggested that $\beta 1$ integrin may play a critical role in mediating cancer growth and metastasis. Therefore, we measured the proportion of $\alpha 5$ integrin⁺ cells or $\beta 1$ integrin⁺ cells in TS/A and MDA-MB-231 cells by flow cytometry. First, TS/A or MDA-MB-231 cells were collected and washed with 1 \times PBS three times. Then, specific monoclonal antibodies for $\alpha 5$ integrin-FITC and $\beta 1$ integrin-FITC were added and co-incubated with cells ($1 \times 10^5/\text{ml}$) at 4°C for 30 minutes. Cells were then washed three times using 1 \times PBS and finally stained with 5 $\mu\text{g}/\text{ml}$ propidium iodide (PI) at 4°C for 10 minutes to exclude dead cells. Cell viability was determined using a flow cytometer (FACSCalibur; BD Bioscience) and CellQuest software. Data showed that 58.67% and 66.19% of TS/A cells were $\alpha 5$ integrin⁺ and $\beta 1$ integrin⁺, respectively. 42.99% and 97.65% of MDA-MB-231 cells were $\alpha 5$ integrin⁺ and $\beta 1$ integrin⁺, respectively (Table 1). Blocking $\beta 1$ integrin signaling pathway with a specific mAb (mouse anti-human integrin beta1 monoclonal antibody; Millipore) could reverse F-HSA's effect on TS/A and MDA-MB-231 breast cancer cell migration (Fig. 8). Taken together, these results indicated that the suppression of breast cancer migration by F-HSA may be mediated by binding of $\beta 1$ integrin.

	$\alpha 5$ integrin	$\beta 1$ integrin
TS/A	58.67 (%)	66.19 (%)
MDA-MB-231	42.99 (%)	97.65 (%)

Table 1. Percentages of $\alpha 5$ integrin⁺ cells and $\beta 1$ integrin⁺ cells in TS/A and MDA-MB-231 cells.

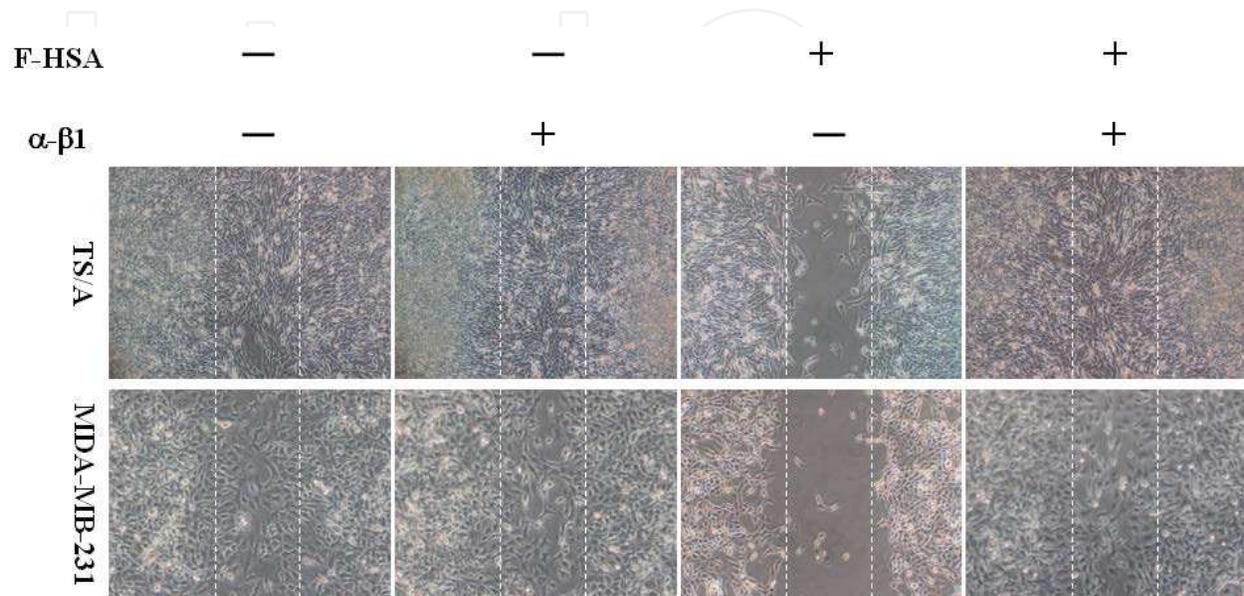


Fig. 8. Blocking the $\beta 1$ integrin signaling pathway with a specific mAb (mouse anti-human integrin beta1 monoclonal antibody) reversed the effect of 0.2 μ M F-HSA on TS/A and MDA-MB-231 breast cancer cell migration.

8. Conclusion

The search for novel therapeutic targets and the development of inhibitors of cancer metastasis is an ongoing challenge. Herein, we used a detergent assisted refolding chromatography process to convert globular HSA into fibrillar F-HSA. Unlike globular HSA, this novel F-HSA caused cell death, reversed EMT, and suppressed breast cancer cell migration through targeting $\beta 1$ integrin signaling pathway. These important findings may be useful for the development of better therapeutics for the intervention of breast cancer metastasis.

9. Acknowledgments

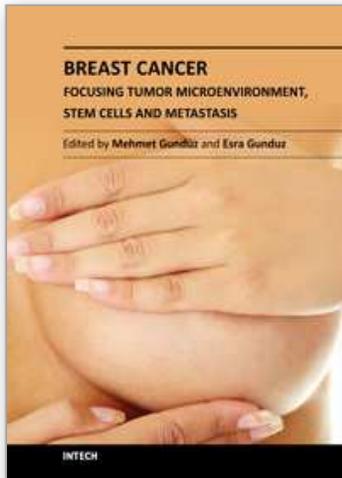
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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