

## Fascin Presents Novel Therapeutic Target for Chemoresistant/Metastatic Breast Cancer

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Received date: May 04, 2016; Accepted date: May 05, 2016; Published date: May 12, 2016

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### Introduction

In recent years, the oncology field has witnessed an unprecedented growth of research and drug development that have led to significant progress in fight against cancer. Despite this progress, the tumor-related mortality remained high mainly due to relapse and metastasis. Therefore, understanding the mechanisms that regulate these processes has been the focus of many research groups and pharmaceutical companies around the globe. Toward this goal, many studies have identified more than one signaling pathways to be involved in regulating cancer cells resistance to conventional therapy and metastasis. Increased activation of the PI3K/AKT and NF- $\kappa$ B signaling have been demonstrated to play major role in making cancer cell resistant to chemotherapy-mediated cell killing and enhancing their metastasis potential [1,2]. Since PI3K/AKT and NF- $\kappa$ B signaling are major pathways that regulate various cellular processes including proliferation, survival and motility [3] and thus developing drugs that target these signaling pathways presents a serious challenge. Instead, many studies focused on identifying genes that have restricted expression in cancer cells and enhance the activity of the PI3K/AKT and NF- $\kappa$ B signaling.

Morphological changes and motility, which are dependents on dynamic actin cytoskeletal rearrangements, are known features for metastatic cancer cells [4]. Fascin is a 55kDa actin bundling protein that is abundantly expressed at certain cellular compartments, which are known to be dynamically involved in regulating cell motility [5]. In normal tissues, fascin expression was reported to be restricted to neurons, endothelial cells and mature antigen presenting dendritic cells [6]. While normal epithelial cells lack fascin, various transformed epithelial cells including breast cancer can express fascin and the level of expression was found to correlate with aggressive tumor phenotype and poor prognosis [7]. In our laboratory, we have demonstrated a liner correlation between the level of fascin in breast cancer patients and the expression of poor prognostic markers including hormone receptor negative (estrogen and progesterone), high histological grade and larger tumor size [8]. Fascin expression in breast cancer samples significantly associated with local and distant metastasis and reduced disease-free survival. Most importantly, fascin expression significantly correlated with suppressed nuclear translocation of breast cancer metastasis suppressor 1 (BRMS1), a tumor suppressor that has been shown to inhibit breast cancer metastasis via targeting the NF- $\kappa$ B pathway [9]. In parallel with fascin-mediated down-regulation of BRMS1, there was up-regulation of NF- $\kappa$ B activity and induction of urokinase-type plasminogen activator and the matrix metalloproteases 2 and 9, metastasis-associated genes that are known to be downstream

targets of the NF- $\kappa$ B. This study provided mechanistic explanation of how fascin expression in breast cancer patients mediates metastasis.

In a subsequent study on animal model and breast cancer samples, we have demonstrated strong correlation between fascin expression and increased breast cancer cell chemoresistance [10]. We found that this fascin-mediated chemoresistance predominantly via amplifying PI3K/Akt activation and FAK phosphorylation, which are known to be major regulators of cell survival. In parallel with the increased PI3K/Akt activity in fascin positive breast cancer cells, which was critical for chemotherapy-mediated apoptotic cell death, there were up-regulation of two inhibitors of apoptosis genes namely XIAP and Livin and suppressed expression of the pro-apoptotic genes caspase 9, caspase 3 and PARP. Based on these findings we proposed different treatment approach of chemoresistant fascin-positive breast cancer patients, where fascin-specific compounds could be combined with PI3K/AKT inhibitors, in conjunction with chemotherapy for more effective treatment.

Chemotherapy can kill most of cancer cells, but spare a small less differentiated subpopulation that possess stem cell-like features, and thus called "Cancer Stem Cells". There is increase interest in understanding the exact phenotype, biology and mechanism that regulate cancer stem cells function in breast cancer. Phenotypically, expression of the ALDH+, CD44hi/CD24lo profile has been linked to breast cancer stem cells [11]. Increased invasion, metastasis and chemoresistance are key features that are linked with the presence of breast cancer stem cells. Our findings of fascin-mediated metastasis and chemoresistance strongly support a role for this protein in regulating the tumor-initiating stem cells. Better understanding of how fascin regulates breast cancer metastasis and chemoresistance will help in designing different therapeutic approaches that can target this protein for more effective treatments.

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