Editorial

Taking aim at a challenging target in pre-clinical models of prostate cancer

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Obesity has become a major health concern in the United States, leading to well-established increased risks for type 2 diabetes and heart disease. Obesity also enhances the risk for several types of cancer (1). Abdominal obesity in particular has been associated with an increased risk for the development of prostate cancer (2), as well as clinically more aggressive disease (2,3). Patients that are obese at the time of diagnosis of multiple different types of cancer, including prostate cancer, demonstrate a higher incidence of chemotherapeutic resistance (1,4). While the majority of cancer therapeutics target the cancer cells, the microenvironment of the tumor has been recognized as a key contributor for cancer progression, metastasis, and development of drug resistance. As such, components of the tumor microenvironment have become an exciting area of investigation to reduce chemotherapy resistance.

Adipose stromal cells (ASCs) have been shown to contribute to the tumor stroma of prostate and other types of cancer (5-7). These cells, located in the adipose tissue depots, have been shown to migrate into tumors (8) and enhance prostate tumor growth and angiogenesis (9,10). Recent work of Su *et al.* demonstrated that ASCs significantly enhanced the aggressive nature of prostate cancer cell lines through induction of epithelial-to-mesenchymal transition (EMT), whereby tumor cells lose their cell polarity and cell-cell adhesion and gain invasive properties and increased mobility (11). When implanted into mice mixed with prostate cancer cells, ASCs enhanced the invasion of the cancer cells from the primary tumor into the surrounding adipose tissue (11). This increased ability for tumor cell invasion is suggestive that the tumor cells have gained the ability to form metastases, however metastatic incidence was not directly examined in this study. These invasive cells could also contribute to residual disease that remains following surgical excision of the primary tumor, leading to localized tumor recurrence. Su *et al.* further demonstrated that ASCs transplanted with prostate tumor cell lines promoted resistance to clinically-used chemotherapeutic agents (11). This work is consistent with other studies examining interactions between ASCs and cancer cells in the lungs and breast (12,13). ASCs may be a particularly important target for improving therapeutics for obese patients. Compared to ASCs from lean mice, ASCs isolated from adipose tissue of obese mice demonstrated increased proliferation, decreased plasticity for differentiation into mesenchymal lineages, and upregulated expression of α-smooth muscle actin, a marker of activated fibroblasts (12). Together these studies suggest that ASCs significantly contribute to aggressive characteristics of prostate tumors that may limit responsiveness to chemotherapeutics.

While ASCs have been shown to enhance tumor growth, targeting ASCs within the tumor microenvironment has had limited success due to few markers to specifically identify these cells. Su *et al.* have pioneered the use of novel killer peptides, which target an ASC-binding domain and demonstrate dose-dependent cytotoxic specificity for ASCs (14,15). Through specificity for non-glycanated decorin (14), the killer peptide D-WAT has efficacy for depletion of a subset of ASCs, which express platelet-derived growth factor beta in both mice and humans (14,16). This form of decorin

appears to be specific to white adipose tissue, and D-WAT does not recognize or deplete mesenchymal stem cells in other organs (17). This killer peptide has also been shown to target ASCs within obese fat depots, leading to reduced white adipose tissue growth (15). Su *et al.* demonstrated that when prostate cancer cells were xenografted into obese and lean mice, D-WAT treatment significantly reduced prostate cancer cell invasion and growth in obese mice compared to vehicle-treated obese and lean mice (11). These results suggest that targeted reduction of ASCs in obese mice reduces aggressive characteristics of the tumors, which may improve response to clinical treatments.

Intriguingly, D-WAT has efficacy on xenografted cancer cell lines on its own, reducing tumor growth in treated mice compared to vehicle-treated mice (16). However, when used in combination with clinically used chemotherapeutics including cisplatin, docetaxel and cabazitaxel, D-WAT significantly reduced tumor cell survival, increased necrosis, and limited tumor volume *in vivo* (11). This suggests that targeting ASCs could significantly enhance the clinical efficacy of chemotherapeutics and potentially reduce therapeutic resistance. In tumor bearing mice, D-WAT treatment led to decreased growth of mammary and Lewis lung carcinoma cells, as well as melanoma (16), suggesting broader clinical utility for this therapeutic agent. Through depletion of ASCs with D-WAT, prostate cancer cells demonstrated reduced expression of markers signifying EMT (11), suggesting that the remaining tumor cells were less invasive and had reduced potential for metastasis. While use of D-WAT reduced the growth of tumor cells with EMT markers during treatment, it is not clear whether treatment with D-WAT can reverse EMT in existing tumor cells. This question is particularly important since tumor cells that have undergone EMT and invaded surrounding tissue would be left following surgical resection of the primary tumor. These pre-clinical studies also focus on late stage disease, which is modeled by the majority of tumor cell lines. D-WAT may also have clinical efficacy for reducing progression of prostatic intraepithelial neoplasia or enhancing responsiveness to first-line hormonal therapies. Continued pre-clinical studies of D-WAT in diverse models will help to address these questions.

While D-WAT has shown pre-clinical success as an adjuvant therapy to increase the response to chemotherapy, there is still considerable investigation necessary. The tumor microenvironment is complex, with multiple other stromal cell types supporting the growth of malignant cells. Functionally, ASCs have been shown to enhance angiogenesis, promote the growth of tumor cell populations with aggressive behavior, and have immunosuppressive properties. Many of these supportive functions of ASCs within the tumor microenvironment have been described for other cell types such as macrophages, myeloid-derived suppressor cells, and endothelial cells. This redundancy of function within the tumor microenvironment has been identified as one mechanism leading to therapeutic resistance of inhibitors and/or antibodies clinically used to target angiogenesis (18). Even within the mesenchymal compartment of the tumor, there is considerable heterogeneity in the complement of markers expressed by cancer-associated fibroblasts (19), and it is currently not clear how these potentially different populations of cells relate to each other. Early clinical trials targeting fibroblast activation protein (FAP)-expressing cancer-associated fibroblasts have not demonstrated efficacy for reducing metastasis in colorectal cancer patients (20,21). However, it is not currently known whether D-WAT also targets FAP-expressing cells or rather a distinct ASC population in the cancer microenvironment. More testing is necessary to determine the timing and/or combinational therapy necessary to maximize potential clinical benefit.

Su *et al.* have presented an exciting pre-clinical model with important implications for improvement of chemotherapeutic response in prostate cancer. Targeting ASCs using D-WAT in the tumor microenvironment may significantly increase therapeutic response in obese prostate cancer patients and potentially other obesity-associated cancers. While the focus of the experiments presented by Su *et al.* demonstrate efficacy of D-WAT in conjunction with clinically used chemotherapy, it is tempting to speculate about other potential therapeutic possibilities. Immunotherapies have not shown similar success and applicability in advanced prostate cancer patients as other types of cancer (22). ASCs have been shown to have immunosuppressive effects in the tumor microenvironment (23), and it is possible that targeted depletion of ASCs could also improve responsiveness to immunotherapy within the tumor microenvironment. Targeting ASCs within the tumor microenvironment could have significant benefit as a cancer therapeutic, and D-WAT may be a new strategy for targeted therapy within the tumor microenvironment.

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Footnote

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