Accepted Manuscript

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PII: S0142-9612(16)30305-2

DOI: 10.1016/j.biomaterials.2016.06.045

Reference: JBMT 17584

To appear in: *Biomaterials*

Received Date: 18 January 2016

Revised Date: 18 June 2016

Accepted Date: 21 June 2016

Please cite this article as: Paholak HJ, Stevers NO, Chen H, Burnett JP, He M, Korkaya H, McDermott SP, Deol Y, Clouthier SG, Luther T, Li Q, Wicha MS, Sun D, Elimination of Epithelial-like and Mesenchymal-like Breast Cancer Stem Cells to Inhibit Metastasis Following Nanoparticle-Mediated Photothermal Therapy, *Biomaterials* (2016), doi: 10.1016/j.biomaterials.2016.06.045.

Elimination of Epithelial-like and Mesenchymal-like Breast Cancer Stem Cells to Inhibit Metastasis Following Nanoparticle-Mediated Photothermal Therapy

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Abstract

Increasing evidence suggesting breast cancer stem cells (BCSCs) drive metastasis and evade traditional therapies underscores a critical need to exploit the untapped potential of nanotechnology to develop innovative therapies that will significantly improve patient survival. Photothermal therapy (PTT) to induce localized hyperthermia is one of few nanoparticle-based treatments to enter clinical trials in human cancer patients, and has recently gained attention for its ability to induce a systemic immune response targeting distal cancer cells in mouse models. Here, we first conduct classic cancer stem cell (CSC) assays, both *in vitro* and in immune-compromised mice, to demonstrate that PTT mediated by highly crystallized iron oxide nanoparticles effectively eliminates BCSCs in translational models of triple negative breast cancer. PTT *in vitro* preferentially targets epithelial-like ALDH+ BCSCs, followed by mesenchymal-like CD44+/CD24- BCSCs, compared to bulk cancer cells. PTT inhibits BCSC self-renewal through reduction of mammosphere formation in primary and secondary generations. Secondary implantation in NOD/SCID mice reveals the ability of PTT to impede BCSC-driven tumor formation. Next, we explore the translational potential of PTT using metastatic and immune-competent mouse models. PTT to inhibit BCSCs significantly reduces metastasis to the lung and lymph nodes. In immune-competent BALB/c mice, PTT effectively eliminates ALDH+ BCSCs. These results suggest the feasibility of incorporating PTT into standard clinical treatments such as surgery to enhance BCSC destruction and inhibit metastasis, and the potential of such combination therapy to improve long-term survival in patients with metastatic breast cancer.

Keywords

Photothermal therapy; Breast cancer stem cells; Iron oxide nanoparticles; Metastasis inhibition; Triple negative breast cancer

1. Introduction