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## ENCAPSULATED HUMAN MESENCHYMAL STEM CELLS (EMSCS) AS A NOVEL ANTI-CANCER AGENT TARGETING BREAST CANCER STEM CELLS: DEVELOPMENT OF 3D PRIMED THERAPEUTIC MSCS

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### SUMMARY

Breast cancer is a leading cause of mortality in women around the globe. The major reason for its recurrence and high mortality is due to the presence of a drug refractory and self-renewing population of cells, the cancer stem cells (CSCs). Mesenchymal stem cells (MSCs) have recently emerged as a promising cell-based therapeutic agent for the treatment of different cancer types. However, the anti-tumor effect of MSCs has been indicated to be substantially reduced by their *in vivo* tumor-trophic migration property and direct cell-to-cell integration with tumor stromal elements. To address this drawback, the present study uses a biomaterial, sodium alginate, for the encapsulation of Wharton's jelly mesenchymal stem cells (WJMSCs) into microbeads, to study the effect of WJMSCs beads on breast CSCs derived from the breast cancer cell lines, MDA-MB-231 and MCF7. Encapsulation with sodium alginate facilitated the prevention of direct cell-to-cell interaction and these microbeads provided a three-dimensional (3D) microenvironment for the encapsulated WJMSCs (eWJMSCs). Compared to two dimensional (2D) culture, eWJMSC increased proliferation of WJMSCs with an increase in pluripotency genes, epithelial to mesenchymal transition (EMT), immune-modulation, and angiogenesis. Interestingly, the tumor invasion suppressor protein E-cadherin was highly expressed in eWJMSCs as shown by Western blot analysis. In addition, eWJMSCs had an increased secretion of anti-inflammatory cytokines VEGF, TGF- $\alpha$ , TNF- $\alpha$ , IFN- $\alpha$ , IL-10 and -6, and IL-3 $\beta$  when compared to 2D culture. Treatment of CSCs with eWJMSCs reduced cell viability, inhibited migration, and exerted an anti-angiogenic effect. eWJMSCs treatment of CSCs increased caspase 3/7 activity, nitride oxide production, and reactive oxygen species production, suggesting its anti-tumorigenic activity. Gene expression analysis revealed that CSCs treated with eWJMSCs had a downregulation of pro-proliferation markers, drug transporters, epithelial-mesenchymal transition-associated markers, and angiogenesis related genes. The mode of anti-proliferative action of WJMSCs beads was possibly through inhibition of the Wnt/ $\beta$ -catenin signaling pathway as indicated by the upregulation of the Wnt antagonists sFRP4 and DKK1. These data suggest that alginate-encapsulated WJMSCs could be an efficient cell contact-free system for developing stem cell-based therapies for CSCs.