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Understanding and harnessing mesenchymal stem cell homing to metastatic prostate cancer

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Prostate cancer (PCa) is the most frequently diagnosed non-cutaneous cancer in Australian men and most PCa-related deaths are associated with metastasis which is currently incurable. Cellular gene therapy utilising bone marrow derived mesenchymal stem cells (BMSC) holds promise as a safe and novel approach for the treatment of PCa. Although our group has identified a unique and safe BMSC subpopulation showing good recruitment to PCa in mice, the distinct receptors and molecular signals required for their homing remain unclear and were explored in this study. GFP tagged BMSC (BMSC-GFP) were infused via the tail vein of syngeneic, immune intact mice in the presence or absence of murine RM1 PCa lung pseudometastases. BMSC-GFP were recruited and persisted within the lungs of RM1-bearing mice alone ($p < 0.01$) when compared to non-tumour bearing mice. Transwell migration assays were employed to further study BMSC homing to PCa *in vitro*. Over 8 hours, BMSCs showed significantly increased migration (2-3 fold) through a semi-porous (8 μ m) membrane in response to RM1 cell conditioned medium (CM), when compared to control medium (MO; $p < 0.05$). BMSC migration was abrogated when CM was pre-treated with proteinase K showing a protein mediated response. For identification of genes involved in homing, BMSC were grown in flasks and exposed to CM or MO. After 8 hours, cells were harvested for RNA isolation and Affymetrix Mouse Gene 1.0 ST microarray profiling. Partek Genomics Suite software identified 63 up-regulated mRNAs in BMSC exposed to CM. Gene ontology analysis revealed a number of these were involved in chemotaxis. Candidate genes PDGFR α , TGF β R3, CXCL5, CXCL2, CCL2 and CCL7 were validated using TaqMan assays and real-time qPCR. This study identified several genes involved in BMSC recruitment to PCa which may be exploited for the development of novel cellular gene therapy strategies for metastatic PCa.

Rosaline Habib is eligible for an AGTS member student prize.