Biological effects of cancer-secreted factors on human mesenchymal stem cells

Paula YP Lam

See related research by Al-Toub et al., http://stemcellres.com/content/4/5/114

Abstract

Mesenchymal stem cells or mesenchymal stromal cells (MSCs) have been considered as a carrier of therapeutic gene because of their inherent ability to migrate to the tumors, and yet there are controversial reports suggesting the tumor-promoting and tumor-inhibiting effects of MSCs. Al-Toub and colleagues provide further insights into the cellular interactions between MSCs and tumors and demonstrate that conditioned media derived from different cancer cells could influence MSC phenotype and gene expression. These changes in MSCs may be modulated by the tumor-derived interleukin-1 beta (IL-1β) and transforming growth factor-beta (TGF-β) signaling.

MSCs possess an innate tropism for injured tissues and tumor cells [6]. This attraction is thought to be mediated through a paracrine signaling loop between the chemotactants from the tumor microenvironment and the expression of the corresponding receptors in MSCs or vice versa. The ability of these MSCs to track pathological lesions and microscopic tumors has posed a significant clinical potential as these cells may potentially be employed for tracking or targeting metastasis and tumors which are inaccessible for resection. As a consequence, many research strategies have been developed to modify MSCs as a cargo of therapeutic genes for cancer gene therapy.

On the flip side of the coin, the impact of MSCs on the development and spread of tumors is poorly understood. MSCs may interact with tumor cells directly or indirectly through the secretion of paracrine factors. MSCs were first demonstrated to enhance the metastatic potency of breast cancer cells, MDA-MB-231 cells, via de novo secretion of the chemokine CCL5 (also known as RANTES, or regulated on activation, normal T cell expressed and secreted) [7]. Mishra and colleagues [8] have independently shown that MSCs exposed to conditioned media from the same MDA-MB-231 breast tumor cells could differentiate into carcinoma-associated fibroblasts and become part of the tumor microenvironment. MSC-derived carcinoma-associated fibroblasts are thought to regulate epithelial-mesenchymal transition (EMT) and tumor-initiating stem cells in tumor [9]. Recently, McGrail and colleagues [10] demonstrated that tumor-secreted soluble factors could promote MSC mobility by inducing cytoskeletal changes through activating the RhoA pathway. However, the precise effect of MSCs from tumor-derived conditioned media (TCM) is unclear. It is also unknown whether all cancer cells exert similar effects on MSCs. In this study, Al-Toub and colleagues demonstrate that MSC responses to TCM are cell line-dependent [1]. Thus, MSCs could either acquire a spindle shape or retain their native cell shape, depending on the types of TCM the MSCs have been exposed to. Gene expression analysis revealed that...
The cooperation of IL-1β cascade, thus increasing the self-renewal capability of tumor cells in clinical therapy. Hence, it is of great importance to advance intra-population heterogeneity and species difference in MSC source and donor variation, and the system is further increased by the environmental signals, adipocytes, and immune cells [14]. The complexity of the stroma consisting of different stromal cells, including tumor cells, tumor-associated fibroblasts, endothelial cells, pericytes, adipocytes, and immune cells [14]. The complexity of the system is further increased by the environmental signals, the difference of MSC source and donor variation, and the intra-population heterogeneity and species difference since most of the preclinical tumorigenesis studies are performed by using human MSCs in immunocompromised rodents. Hence, it is of great importance to advance our understanding of MSC biology before implementation in clinical therapy.

Abbreviations
EMT: Epithelial-mesenchymal transition; IL-1β: Interleukin-1 beta; MHC: Major histocompatibility complex; MSC: Mesenchymal stem cell; TCM: Tumor-derived conditioned media; TGF-β: Transforming growth factor-beta.

Competing interests
The author declares that she has no competing interests.

Acknowledgments
PYPL is supported by the National Medical Research Council, Singapore (NMRC/1201/2009 and NMRC/CG/007/2013).

Author details
1Laboratory of Cancer Gene Therapy, Cellular and Molecular Research Division, Humphrey Oei Institute of Cancer Research, National Cancer Centre, 11, Hospital Drive, Singapore 169610, Singapore. 2Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, 21 Lower Kent Road, Singapore 119077, Singapore. 3Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857, Singapore.

References
1. Al-Toub M, Alnosa A, Almajed M, Al-Nbaheen M, Kassem M, Aljahmas A, Al-Aqeel AM: Pleiotropic effects of cancer cells’ secreted factors on human stromal (mesenchymal) stem cells. Stem Cell Res Ther 2013, 4:14.
2. Friedenstein AJ, Chailakhjan RK, Lalykina KS: The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet 1970, 3:393–403.
3. Barry FP, Murphy JM, English K, Mahon BP: Immunogenicity of adult mesenchymal stem cells: lessons from the fetal allograft. Stem Cells Dev 2005, 14:252–265.
4. Qi Y, Feng G, Yan W: Mesenchymal stem cell-based treatment for cartilage defects in osteoarthritis. Mol Biol Rep 2012, 39:5683–5689.
5. Uccelli A, Prockop DJ: Why should mesenchymal stem cells (MSCs) cure autoimmune diseases? Curr Opin Immunol 2010, 22:768–774.
6. Chan JK, Lam PY: Human mesenchymal stem cells and their paracrine factors for the treatment of brain tumors. Cancer Gene Ther 2013, 20:539–543.
7. Kamnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA: Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 2007, 449:557–563.
8. Mishra PJ, Mishra PJ, Humeniuk R, Medina DJ, Alexe G, Mesirov JP, Ganesar S, Gidiot JW, Banerjee D: Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. Cancer Res 2008, 68:4331–4339.
9. Polyak K, Weinberg RA: Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. Nat Rev Cancer 2009, 9:265–273.
10. McGail DJ, Ghosh D, Quach ND, Dawson MR: Differential mechanical response of mesenchymal stem cells and fibroblasts to tumor-secreted soluble factors. PLoS One 2012, 7:e33348.
11. Camero R, Gerra I, Lledó E, Dopazo J, García-Garcia F, Rubio MP, Trigueros C, Dorronsoro A, Ruiz-Sauri A, Montero JA, Sepulveda P: IL1β induces mesenchymal stem cells migration and leukocyte chemotaxis through NF-κB. Stem Cell Rev 2012, 8:905–916.
12. Ho IA, Toh HC, Ng WH, Teo YL, Guo CM, Hui KM, Lam PY: Human bone marrow-derived mesenchymal stem cells suppress human glioma growth through inhibition of angiogenesis. Stem Cells 2013, 31:146–155.
13. Wang L, Liu Z, Bollwoda S, Shrestha T, Bossmann S, Pyle M, Pappan L, Shi J, Troyer D: Interleukin-1β and transforming growth factor-β cooperate to induce neurosphere formation and increase tumorigenicity of adherent LN-229 glioma cells. Stem Cell Res Ther 2012, 3:5.
14. Albiní A, Sporn MB: The tumour microenvironment as a target for chemoprevention. Nat Rev Cancer 2007, 7:139–147.

Published: 15 Nov 2013

Cite this article as: Lam: Biological effects of cancer-secreted factors on human mesenchymal stem cells. Stem Cell Res Ther 2013, 4:138