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COMMENTARY

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

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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.

A report from Al-Toub and colleagues [1] in the previous issue of *Stem Cell Research & Therapy* provides further insights into how cancer influences the biological properties of human mesenchymal stem cells. Mesenchymal stem cells or mesenchymal stromal cells (MSCs) were first described by Friedenstein and colleagues [2] as plastic-adherent, non-hematopoietic stromal cells (approximately 0.0001% to 0.001% of the nucleated cells) in the bone marrow and later were identified in many tissue types. The multipotent potential of MSCs makes them an excellent cell source for regenerative medicine. MSCs are poorly immunogenic because of low expressions of major histocompatibility complex (MHC) class I and absence of MHC class II [3]. Thus, MSCs have been used in clinical trials for the treatment of many diseases, including cartilage and bone injury [4] and inflammation-associated disorders [5].

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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 chemoattractants 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

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tumor-derived interleukin-1 beta (IL-1β) is one of the factors responsible for the differential morphological changes. Treatment of MSCs with recombinant IL-1β mimicked the effects of TCM on MSCs via the focal adhesion kinase and, to a lesser extent, mitogen-activated protein kinase pathways. These biological effects may be counteracted through pharmacological inhibition of the transforming growth factor-beta (TGF-β) signaling in MSCs in the presence of TCM. These findings provide support that the transition of MSCs to myofibroblast is modulated by multiple signaling ligands that interact directly or indirectly via the TGF-β signaling cascade.

Further investigations are required to understand the differential effect of TCM on MSCs. It is interesting that IL-1β is one of the mediators of the pro-inflammatory phenotype observed in MSCs exposed to TCM. Carrero and colleagues [11] have demonstrated that IL-1β increases migration and adhesion of MSCs and promotes leukocyte chemotaxis through soluble factors secreted by MSCs. The anti-tumor effect of MSCs on glioma has also been shown to inhibit IL-1β signaling which significantly impaired tumor angiogenesis via modulation of cathepsin B expression [12]. Alternatively, tumor-derived IL-1β could promote MSCs to undergo EMT by modulating the TGF-β signaling cascade, thus increasing the self-renewal capability of tumor cells. The cooperation of IL-1β and TGF-β has been shown to promote the neurosphere formation in glioma [13].

However, the tumor microenvironment is complex, 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.

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