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Therapeutic potential of transgenic mesenchymal stem cells engineered to mediate anti–high mobility group box 1 activity: targeting of colon cancer

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ABSTRACT

Background: Mesenchymal stem cells (MSCs) are being developed as a new clinically relevant stem cell type to be recruited into and to repair injured tissue. A number of studies have focused on the therapeutic potential of MSCs by virtue of their immunomodulatory properties. Systemically administered MSCs can also migrate to sites of malignancies. Because of this latter phenomenon, we transfected human MSCs to secrete anti–high mobility group box (HMGB) 1 proteins. They were then injected into mice bearing human colon cancer to evaluate their efficacy as an antineoplastic agent.

Materials and methods: The ABOX gene was used in this model, which encodes part of the HMGB1 protein and acts as an HMGB1 antagonist. It was cotransduced by electroporation with a FLAG-tag to visualize the secreted ABOX protein, levels of which in supernatants from cultured transfected MSCs were quantified by immunofluorescence imaging using an anti-FLAG antibody. Antiangiogenic effects were evaluated *in vitro* using a novel optical assay device for the quantitative measurement of cellular chemotaxis assessing the velocity and direction of endothelial cell movement stimulated by supernatant from tumor cells. We found that ABOX proteins released from transfected MSCs suppressed migration in this assay. Finally, MSCs were injected subcutaneously into Nonobese diabetic/severe combined immunodeficiency mice bearing human colon cancer from a cell line, which secreted large amounts of HMGB1. Ten days after MSC injection, mice were sacrificed and tumors evaluated by immunohistochemistry.

This is an AAS article. In addition, the author would like to apply for the AAS awards of the BEST OVERALL MANUSCRIPT and the BEST MANUSCRIPT BY A NEW AAS MEMBER.

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Results: From 12 ho through 7 d after gene transfection, ABOX proteins secreted from MSCs could be detected by immunofluorescence and enzyme-linked immunosorbent assay. Quantitative measurement of cellular chemotaxis demonstrated that ABOX proteins secreted from transfected MSCs decreased the velocity and interfered with the direction of movement of vascular endothelial cells. Moreover, in an *in vivo* human colon cancer xenograft model, injection of anti-HMGB1–transfected MSCs resulted in a decreased tumor volume due to the antiangiogenic properties of the secreted ABOX proteins.

Conclusions: MSC modified to secrete HMGB1 antagonist proteins have therapeutic antineoplastic potential. These findings may contribute to future novel targeting strategies using autologous bone marrow–derived cells as gene delivery vectors.

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1. Introduction

Mesenchymal stem cells (MSCs) are one of the multipotent cell types capable of differentiating into several mesenchymal phenotypes such as adipocytes, osteoblasts, chondrocytes, myocytes, and fibroblasts [1]. They secrete a plethora of cytokines, chemokines, and growth factors [2], without complicated culturing or handling techniques. They have strong migration capacity into inflamed tissues and tumors, because of their expression of the appropriate receptors [3]. Thus, MSCs may potentially be used for cell-based therapies and could be considered a clinically relevant cell type for therapeutic application. The migration of MSCs into different type of inflamed or injured tissues has been studied in several models [4,5]. Indeed, isolated MSCs from bone marrow have been demonstrated to migrate toward inflamed tissues and exert their effects *via* direct contact or in a paracrine fashion in response to inflammatory cells such as macrophages [6,7], dendritic cells [8,9], and T-cells [5,10]. Recently, there has been heightened interest in the migration capacity of MSCs and their homing into tumors. Because tumor progression is closely related to inflammation and epithelial-mesenchymal transition is critical in cancer progression [11], the role of MSCs in carcinogenesis has emerged as an attractive new concept in cancer therapy. Although there is abundant experimental evidence supporting the therapeutic potential of MSCs, the mechanism of homing and recruitment of these cells into tumors and their potential role in malignant tissue progression is still not well understood. Indeed, in some studies, MSCs have been shown to promote tumor development by immune modulation [12], whereas other studies reported that MSCs have a suppressive effect on tumor development; for example, *via* modification of Akt signaling [13]. The discrepancy between these results may be due to the use of different tissue sources, individual donor variability, and the timing of MSC injection. The expression of important receptors such as Toll-like receptor (TLR) differs at different time points during treatment [14], which may also influence the effect of MSCs on tumor development. Whether MSCs support or suppress the tumor, it is apparent that systemically or even locally administered MSCs can be recruited by and migrated toward tumors [15,16]. Very recently, we demonstrated that MSCs have the potential to migrate toward colon cancer cells and the tumors derived from them, as shown using a quantitative optical migration assay and in a tumor-bearing mouse model [17]. These findings are important because they can form the basis for studies to investigate the utilization of engineered MSCs as novel carriers for delivery of antitumor agents to malignancies, for the development of tumor-targeted therapies. In fact, several reports have described that MSCs could be genetically modified to secrete different anticancer molecules such as tissue necrosis factor (TNF) [18], TNF-related apoptosis-inducing ligand [15] or interferon β [16]. Interestingly these engineered MSCs were able to decrease tumor progression.

Numerous different mediators have been reported to be involved in the recruitment of MSCs [19–21]. Growth factors, chemokines, or cytokines have already been described as mediators that can regulate cell migration toward inflamed tissues, for example, SDF-1, interferonγ, CCL5/CCR5, CCR2, TNF-α, and some other peptides [22–26]. Among these molecules, Meng *et al.* [27] highlighted high mobility group box 1 (HMGB1) protein, considered to be a proinflammatory and also tumor-related cytokine, as a mediator, which could modulate the biological capacities of MSCs. HMGB1 is responsible for several autocrine and/or paracrine feedback mechanisms resulting in positive regulation of its expression. Its receptor, TLR4, is expressed by MSCs [28]. Recently, we reported that MSC recruitment into colon cancers depended on HMGB1 secretion by the tumor [17]. Consistent with this, there is a report that HMGB1 induced the secretion of vascular endothelial growth factor and platelet-derived growth factor from tumor cells. Thus, HMGB1 has been identified as an important modulator of tumor angiogenesis [29]. Indeed, when one of the receptors for HMGB1, the receptor for advanced glycation end products (RAGE), is inhibited systemically, tumor growth may be significantly suppressed [30].

To develop an efficient antitumor agent, we investigated one of the HMG-box domains, ABOX, which acts as an antagonist of HMGB1 [31]. ABOX binds RAGE, and might inhibit the effects of HMGB1 as an inflammatory cytokine and as a modulator of tumor angiogenesis *in vivo*. Indeed, there are several reports focusing on anti-inflammatory effects of ABOX. For example, ABOX attenuated sepsis in a mouse peritonitis model [31] and reduced brain damage caused by ischemia [32]. This ABOX protein is available from HMGBiotech in Milano, Italy. In the present study, we tested whether transfecting the gene for this protein into human MSC (ABOX-hMSC) resulted in antineoplastic effects mediated by the cells. ABOX-hMSCs was found to modulate endothelial cell migration and reduce tumor progression by inhibiting tumor angiogenesis in an animal model of human colon cancer.

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