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Placenta-derived mesenchymal stem cells and their secreted exosomes inhibit the self-renewal and stemness of glioma stem cells *in vitro* and *in vivo*

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Mesenchymal stromal cells (MSCs) can be obtained from various sources, easily expanded in vitro for therapeutic applications and their safety and therapeutic impact have been demonstrated in various pre-clinical and clinical studies. MSCs have been shown to cross the blood brain barrier and migrate to sites of experimental GBM and can deliver cytotoxic compounds that exert anti-tumor effects. Here, we examined the effects of placenta-derived MSCs and their secreted exosomes on GSC stemness and oncogenic potential *in vitro* and *in vivo*. Placenta MSC-derived exosomes decreased the self-renewal, stemness markers, Nanog and Oct4 and the migration of these cells. Similarly, intracranial administration of the MSCs decreased the tumor volume of GSC-derived xenografts and prolonged animal survival. miRNA sequence analysis of placenta MSC-derived exosomes revealed a set of specific miRNAs that were downregulated in GSCs and that acted as tumor suppressors in these cells. We demonstrated delivery of some of these miRNAs to GSCs following treatments with MSC-derived exosomes. We further demonstrated that MSCs or exosomes that were loaded with exogenous miR-124 delivered high levels of this miRNA into glioma cells as detected by a novel quantitative miRNA reporter. Moreover, administration of placenta MSCs loaded with exogenous miR-124 exerted a strong inhibitory effect on GSC-derived xenograft growth. These results demonstrate that placenta-derived MSCs may have important clinical applications in stem cell-based glioma therapeutics. Moreover, these studies provide a novel approach for the targeted delivery of endogenous and exogenous anti-tumor miRNAs to glioma cells as a miRNA replacement therapy for GBM.

Biography

Chaya Brodie has completed her PhD at 1998 from Bar-Ilan University and postdoctoral studies at University of Colorado and National Jewish Center for Immunology and Respiratory Medicine. She is a Senior Staff Scientists at the Henry Ford Hospital and a Professor in the Faculty of Life Sciences, Bar-Ilan University, Israel. She has published more than 135 papers in reputed journals and has been serving as a reviewer in various NIH study sections and in international foundations and societies.

Mesenchymal stem cells as carriers and amplifiers in CRAd delivery to tumors

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Background: Mesenchymal stem cells (MSCs) have been considered to be the attractive vehicles for delivering therapeutic agents toward various tumor diseases. This study was to explore the distribution pattern, kinetic delivery of adenovirus, and therapeutic efficacy of the MSC loading of E1A mutant conditionally replicative adenovirus Adv-Stat3(-) which selectively replicated and expressed high levels of anti-sense Stat3 complementary DNA in breast cancer and melanoma cells.

Methods: We assessed the release ability of conditionally replicative adenovirus (CRAd) from MSC using crystal violet staining, TCID(50) assay, and quantitative PCR. *In vitro* killing competence of MSCs carrying Adv-Stat3(-) toward breast cancer and melanoma was performed using co-culture system of transwell plates. We examined tumor tropism of MSC by Prussian blue staining and immunofluorescence. *In vivo* killing competence of MSCs carrying Adv-Stat3(-) toward breast tumor was analyzed by comparison of tumor volumes and survival periods.

Results: Adv-Stat3(-) amplified in MSCs and were released 4 days after infection. MSCs carrying Adv-Stat3(-) caused viral amplification, depletion of Stat3 and its downstream proteins, and led to significant apoptosis in breast cancer and melanoma cell lines. *In vivo* experiments confirmed the preferential localization of MSCs in the tumor periphery 24 hours after tail vein injection, and this localization was mainly detected in the tumor parenchyma after 72 hours. Intravenous injection of MSCs carrying Adv-Stat3(-) suppressed the Stat3 pathway, down-regulated Ki67 expression, and recruited CD11b-positive cells in the local tumor, inhibiting tumor growth and increasing the survival of tumor-bearing mice.

Conclusions: These results indicate that MSCs migrate to the tumor site in a time-dependent manner and could be an effective platform for the targeted delivery of CRAd and the amplification of tumor killing effects.