Investigation of the Effects of B16F10 Derived Exosomes in Induction of Immunosuppressive Response in the Stem cells

Abstract

One of the main mechanisms of tumor cells' escape from destruction by the immune system is the suppression of antitumor immune responses. Myeloid-derived suppressor cells (MDSCs) are the main immunosuppressive cells present in the tumor microenvironment (TME) that sustain tumor progression. MDSCs are a heterogeneous group of cells including granulocytic MDSC (G-MDSCs) and monocytes MDSC (Mo-MDSCs) which originate from immature myeloid cells. Tumor cell-derived exosomes (TEX) can deliver their cargoes to myeloid cells and convert them into MDSC. Herein, the researchers investigated the effects of exosomes from B16F10 mouse melanoma cells on the development of hematopoietic stem cells (HSC) into MDSC subtypes. Briefly, the exosomes were isolated from the cultured B16F10 cell line. We isolated HSC from the C57BL6 mouse model of melanoma cancer. Differentiation of the HSC into the MDSC was done through the treatment of the HSC with exosomes. To confirm the differentiation of the HSC cells, the researchers performed the expression of markers of MDSC with flow cytometry. In addition, we measured the cytokine secretion in the supernatant with ELISA. After co-incubation, the flow cytometry analysis implied higher percentages of CD11b +, Ly6G + and Ly6C+ cells in exosome treated HSC group compared to untreated HSC group. The percentage of CD11b +, Ly6G + cells was more than CD11b +, Ly6C+ cells in exosome treated HSC group. Besides, IL10 and TGFβ expressions in treated HSC increased in comparison to HSC cultured alone. This study demonstrates that TEX acts as key regulators of tumor suppression by having effects on the differentiation of HSC. Therefore, they can be attractive candidates for immunomodulatory cell-free therapy for melanoma.

Exosomes are small extracellular vesicles (sEVs), playing a crucial role in the intercellular communication in physiological as well as pathological processes. Here, we aimed to study whether the melanoma-derived sEV-mediated communication could adapt to microenvironmental stresses. We compared B16F1 cell-derived sEVs released under normal and stress conditions, including cytostatic, heat and oxidative stress. The miRNome and proteome showed substantial differences across the sEV groups and bioinformatics analysis of the obtained data by the Ingenuity Pathway Analysis also revealed significant functional differences. The in silico predicted functional alterations of sEVs were validated by in vitro assays. For instance, melanoma-derived sEVs elicited by oxidative stress increased Ki-67

expression of mesenchymal stem cells (MSCs); cytostatic stress-resulted sEVs facilitated melanoma cell migration; all sEV groups supported microtissue generation of MSC-B16F1 co-cultures in a 3D tumour matrix model. Based on this study, we concluded that (i) molecular patterns of tumour-derived sEVs, dictated by the microenvironmental conditions, resulted in specific response patterns in the recipient cells; (ii) in silico analyses could be useful tools to predict different stress responses; (iii) alteration of the sEV-mediated communication of tumour cells might be a therapy-induced host response, with a potential influence on treatment efficacy.

BIOGRAPHY

Mohammad Reza Atashzar has expertise in immunology and stem cell and cancer immunotherapy. I received PHD of immunology from Shahid beheshti university of medical sciences, Tehran, Iran.

Email: mr.atashzar@yahoo.com