MELANOMA CELL DERIVED EXOSOMES ALTER THE MICROENVIROMENT OF MALIGNANT TUMORS VIA RE-EDUCATION OF MESENCHYMAL STEM CELLS BY miRNAs

Gyukity-Sebestyén Edina [1]

Harmati Mária [1], Dobra Gabriella[1], Marton Annamária [1] Katona L. Róbert [1], Horváth Péter[1], Nagy István [1], Vizler Csaba[1], Buzás Krisztina [1,2]

1 Hungarian Academy of Sciences, Biological Research Centre, Szeged, Hungary

2 University of Szeged, Faculty of Dentistry, Szeged, Hungary

Intoduction

Malignant melanoma is the most aggressive skin cancer. The mechanism of its rapid metastasis formation, high genetic variability and effective immune escape mechanisms are not explained yet. Exosomes are among the potential mediators of communication between melanoma cells and their environment. To explore the interaction of melanoma cell derived exosomes (mcde) and their microenvironment, we investigated their effect on mesenchymal stem cells (MSC).

Materials and methods

Murine primary MSCs from adipose tissue were pretreated with B16F1 melanoma cell derived exosomes. Exosomes were stained by lipidophilic dyes and their uptake into recipient cells was visualised. Then the rate of spontaneous apoptosis and expression of multipotent stromal cell markers were analyzed by flow cytofluorometry.

To explore the potential *in vivo* tumor-promoting effect of exosomes, B16F1 tumor bearing mice were injected with mcde-conditioned MSCs i.v.; the control mice received untreated MSC.

Because we hypothesized that the significant component of exosomal information packages are the carried miRNA content, we sequenced the whole miRNA spectra by SOLiD 5500xl technology, and then the sequences were annotated in CLC Genomics Workbench version 5.5.1.

Results

After 1 hour incubation we have observed that the labeled exosomes internalized into MSCs. The exosome internalization was the highest after 4 hours treatment.

We have found marked differences in the expression CD44, α4 integrin, CD29, CD106, CD73 and Sca-1 after induction. The ratio of late apoptotic or necrotic/early apoptototic cells decreased after mcde treatment (0.43/1 *versus* 0.98/1).

In animal experiments, the survival rate at day 42th was 38% after mcde-conditioned MSC treatment *versus* 85% non conditioned MSCs.

We have found highest expression levels of mir205, mir31, mir21a, mir15b, respectively.

Conclusion

Our data suggest that melanoma cell derived exosomes could re-educate mesenchymal stem cells, giving rise to a cell population that supports metastasis formation. The potential inducer of MSC re-education might be the miRNA content of exosomes.

Az abstract témája elméleti jellegű, előadás formájában szertném prezentálni.