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Exosomes, proteomics and cell surface markers in CML

Exosomes are small extracellular vesicles with size ranging from 30 to 150 nm. Exosomes act within cell to cell communication in various physiological and pathological processes, mediating transport of proteins, lipids, mRNA, miRNA and DNA. Recent publications link exosomes newly with processes of cancer progression and acquired drug resistance. Emerging studies performed on various models of cancer diseases describe exosomes playing role in angiogenesis, metastasis, immunosuppression and malignant cell transformation. Other published works show ability of exosomes to sequestrate anticancer drug, making it less available for treatment of cancer cells, thus contributing to drug resistance. In order to examine the role of exosomes in drug resistance we performed a pilot study using cell line of chronic myeloid leukemia (CML), which is currently being cured by TKI inhibitors such as imatinib. We derived imatinib resistant cells from model K562 cell line and isolated exosomes released by these cells. Our recently published data show that exosomes derived from imatinib resistant cells are intercepted by the original imatinib sensitive K562 CML cells and increase their survival in the presence of the TKI drug imatinib. Thus, our study suggests that exosomes play a role in drug resistance transfer between cells in CML (Fig.1) [1].

We investigated exosomal protein composition to elucidate putative mechanism of drug resistance transfer which may affect receiving cells. By label free mass spectrometry we compared protein content of exosomes isolated from imatinib sensitive and resistant cells. We identified over 3000 individual proteins, from which at least 35 were differently abundant. For example, we identified three membrane proteins (IFITM3, CD146 and CD36) to be upregulated in exosomes from imatinib resistant CML cells. Expression of these three proteins was also highly increased in imatinib- resistant cells when verified by western blot (Fig.2) [1] and further confirmed by flow cytometry analysis (FACS).

Identification of resistance associated surface markers in exosomes and cells could contribute to early diagnostics of drug resistance in CML/cancer therapy. Targeting the potential markers of resistance carried by exosomes with clinically available inhibitors could also prevent spreading of drug resistance between cells. We suggest that our approach in exosome research is relevant for future diagnostics and personalized therapy in drug resistant CML and other cancer diseases in general.

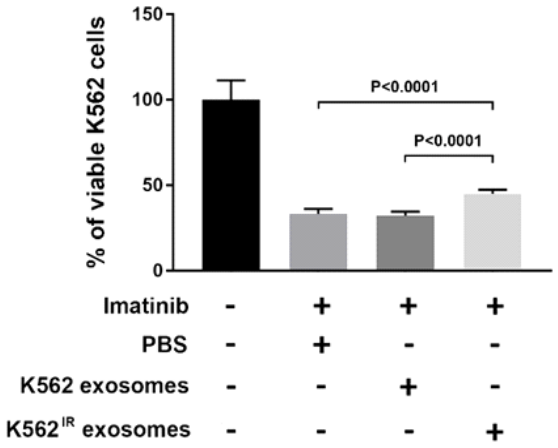

Fig.1 Exosomes released from Imatinib-resistant CML cells ($K562^{IR}$) potentiate survival of Imatinib-sensitive K562 cells in the presence of Imatinib.

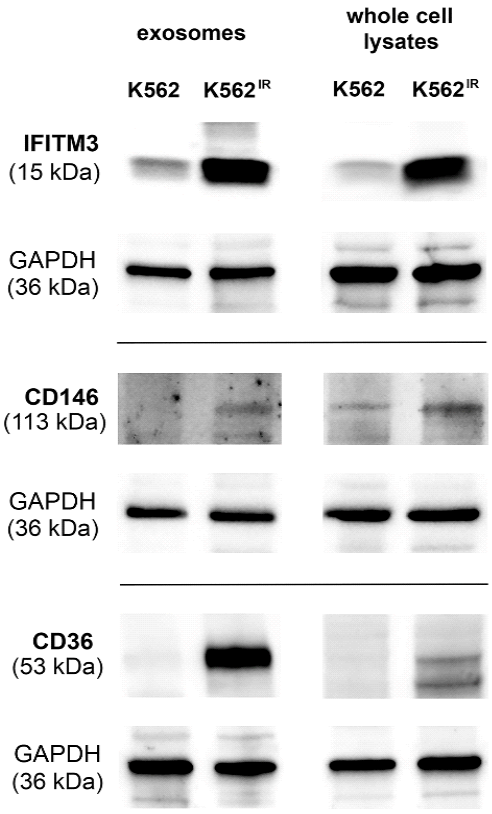

Fig. 2 Differential expression of surface markers of imatinib resistance in exosomes and whole cell lysates as confirmed by specific antibodies. K562 – imatinib sensitive cells and exosomes, $K562^{IR}$ – imatinib resistant cells and exosomes

Publication:

1. Hrdinova T, Toman O, Dresler J, Klimentova J, Salovska B, Pajer P, Bartos O, Polivkova V, Linhartova J, Machova Polakova K, Kabickova H, Brodska B, Krijt M, Zivny J, Vyoral D, Petrak J. Exosomes released by imatinib-resistant K562 cells contain specific membrane markers, IFITM3, CD146 and CD36 and increase the survival of imatinib-sensitive cells in the presence of imatinib. Int J Oncol. 2021 Feb;58(2):238-250. doi: 10.3892/ijo.2020.5163. Epub 2020 Dec 23.PMID: 33491750