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СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭКЗОСОМ КЛЕТОК ЭСТРОГЕН-РЕЗИСТЕНТНОГО РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

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Аннотация

Участие экзосом в патогенезе злокачественных опухолей основано на их способности проникать внутрь клеток-реципиентов, вызывая в последних каскад генетических и эпигенетических изменений. Ранее мы показали, что экзосомы, продуцируемые различными вариантами эстроген-независимых сублиний клеток рака молочной железы (MCF-7/T, полученной в результате длительного культивирования клеток в присутствии антиэстрогена тамоксифена, и MCF-7/M, полученной в результате культивирования клеток с метформинном), способны индуцировать резистентность в родительских клетках MCF-7. В настоящей работе для исследования характерных особенностей состава экзосом резистентных клеток был проведен сравнительный анализ протеома и профиля микроРНК контрольных экзосом и экзосом, полученных от резистентных сублиний. В целом в образцах экзосом было идентифицировано более 400 белков, из которых только 2 белка, DMBT1 (Deleted in Malignant Brain Tumors 1) и THBS1 (Thrombospondin-1), были гиперэкспрессированы в обоих типах резистентных экзосом (менее 5 % от общего количества белков, дифференциально экспрессированных в экзосомах резистентных клеток), что свидетельствует об уникальном составе экзосомальных белков для каждого типа резистентных клеток. Сравнительный анализ состава микроРНК, дифференциально экспрессированных в обоих вариантах экзосом резистентных клеток, выявил 180 гиперэкспрессированных микроРНК и 202 микроРНК с пониженной экспрессией. Среди них 4 гиперэкспрессированных и 8 гипоекспрессированных микроРНК оказались ассоциированы с развитием гормональной резистентности клеток рака молочной железы. Биоинформатический анализ 4 гиперэкспрессированных микроРНК выявил 2 микроРНК, miR-101 и miR-181b, участвующих в стимуляции PI3K сигналинга, свидетельствуя о важной роли последнего в развитии гормональной резистентности клеток рака молочной железы.

Ключевые слова: рак молочной железы, тамоксифен, экзосомы, гормональная резистентность, микроРНК.

COMPARATIVE ANALYSIS OF THE EXOSOMAL CARGO OF THE ESTROGEN-RESISTANT BREAST CANCER CELLS

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Abstract

The exosomes involvement in the pathogenesis of tumors is based on their property to incorporate into the recipient cells resulting in the both genomic and epigenomic changes. Earlier we have shown that exosomes from different types of estrogen-independent breast cancer cells (MCF-7/T developed by long-term tamoxifen treatment, and MCF-7/M) developed by metformin treatment were able to transfer resistance to the parent MCF-7 cells. To elucidate the common features of the both types of resistant exosomes, the proteome and microRNA cargo of the control and both types of the resistant exosomes were analyzed. Totally, more than 400 proteins were identified in the exosome samples. Of these proteins, only two proteins, DMBT1 (Deleted in Malignant Brain Tumors 1) and THBS1 (Thrombospondin-1), were commonly expressed in the both resistant exosomes (less than 5% from total DEPs) demonstrating the unique protein composition of each type of the resistant exosomes. The comparative analysis of the miRNA differentially expressed in the both MCF-7/T and MCF-7/M resistant exosomes revealed 180 up-regulated and 202 down-regulated miRNAs. Among them, 4 up-regulated and 8 down-regulated miRNAs were associated with progression of hormonal resistance of breast tumors. The bioinformatical analysis of 4 up-regulated exosomal miRNAs revealed 2 miRNAs, mir-101 and mir-181b, which up-regulated PI3K signaling supporting the key role of PI3K/Akt in the development of the resistant phenotype of breast cancer cells.

Keywords: breast cancer, tamoxifen, exosomes, hormonal resistance, microRNA.

Exosomes are 30-100 nm-sized microvesicles that are generated in the cells and released into the extracellular space accumulating in many biological fluids, including urine, milk, semen, cerebrospinal fluid, lymph, saliva, etc. [1]. It is noteworthy that tumor cells produce much more exosomes than normal cells [2]. The exosomes involvement in the pathogenesis of tumors is based on their property to incorporate into the recipient cells resulting in the both genomic and epigenomic changes [3-8]. Recently, the ability of the exosomes secreted by the drug- or hormone-resistant tumor cells to transfer the resistant properties to recipient cells has been demonstrated in different cell models [9, 10].

The main goal of the present study was to analyse the features of the exosomes of the estrogen-resistant breast cancer cells and to identify the exosomal factors responsible for transferring of the resistant phenotype to the donor cells.

Earlier, using the estrogen-dependent MCF-7 breast cancer cells and estrogen-independent MCF-7/T cells we have demonstrated the ability of the resistant cells-derived exosomes to initiate the estrogen-independent growth of the parent MCF-7 cells. The parallel experiments were performed on the MCF-7/M resistant subline developed under long-term cultivation of the parent MCF-7 cells with biguanide metformin and characterized by the cross-resistance to metformin and tamoxifen. The treatment of the parent MCF-7 cells with the MCF-7/M exosomes resulted in the cell cross-resistance to metformin and tamoxifen. Both types of resistant exosomes, MCF-7/T and MCF-7/M, induced the similar changes in the cell signaling: inhibition of the estrogen signaling and stimulation of the Akt protein kinase and transcription factors AP-1 and NF- κ B [11].

Here, to elucidate the common features of the both types of resistant exosomes, the proteome and microRNA cargo of the control and both types of

the resistant exosomes were analyzed. Exosomes were prepared from the MCF-7, MCF-7/T and MCF-7/M conditioned medium by the differential ultracentrifugation, and exosome imaging was carried out by transmission electron microscope. For proteome study, an AB Sciex 5800 MALDI TOF/TOF mass spectrometer (Sciex, Germany) was used. Analysis of MS and MS/MS spectra was done with Protein Pilot software using the UniProtKB/SwissProt/NCBI international protein databases. Then the differentially expressed proteins in the exosomes of MCF-7, MCF-7/T and MCF-7/M cells were detected. Totally, more than 400 proteins were identified in the exosome samples. Among them, 131 differentially expressed proteins (DEPs) were found in the exosomes of MCF-7/T cells versus MCF-7 exosomes and 97 DEPs were found in the MCF-7/M exosomes.

To find the common changes in the proteome of the resistant exosomes, DEPs in the exosomes from MCF-7/T and MCF-7/M cells were compared. As revealed, only two proteins, DMBT1 (Deleted in Malignant Brain Tumors 1) and THBS1 (Thrombospondin-1), were commonly expressed in the both resistant exosomes (less than 5% from total DEPs) demonstrating the unique protein composition of each type of the resistant exosomes. Noteworthy, the bioinformatical analysis showed correlation between expression of two identified proteins and breast cancer risk. Namely, single-nucleotide polymorphisms (SNPs) and overexpression of DMB1 were found to be associated with the breast cancer [12, 13]. Several studies demonstrated that high level of THBS1 mediates chemotherapy resistance through the integrin β 1/mTOR pathway [14] and promotes aggressive phenotype via epithelial-mesenchymal transition (EMT) [15].

The analysis of exosomal microRNAs was performed by HiSeq2500 and at least 5 million reads per samples were obtained. Library preparation

Table 1

Differentially expressed miRNAs in the exosomes of the resistant MCF-7/T and MCF-7/M cells

Cell line	Total miRNAs	Up-regulated miRNAs	Down-regulated miRNAs
MCF-7/T	877	459	418
MCF-7/M	751	388	363
Common miRNAs	382	180	202

Table 2

Differentially expressed exosomal miRNAs associated with hormonal resistance

Up-regulated miRNAs	Biological effects	Refs
hsa-miR-101-3p	Upregulates the phosphorylated Akt (pAkt)	[16]
hsa-miR-210-5p	Up-regulated in TAM-R MCF-7	[17]
hsa-miR-7704	Up-regulated in TAM-R MCF-7	[18]
has-miR-181b	Up-regulated in TAM-R MCF-7cells	[19]
Down-regulated miRNAs	Biological effects	Refs
hsa-let-7b-3p	Induce tamoxifen sensitivity by downregulation of estrogen receptor	[20]
hsa-miR-10a-3p	Suppresses the levels of p-Akt, p-mTOR, p-p70S6K, and PIK3CA, and increases the expression of Cyt C, cleaves caspase-3, and the ratio of Bax/Bcl-2	[21]
hsa-miR-148a-3p	Increase drug sensitivity of breast cancer cells	[22]
hsa-miR-182-5p	Induces apoptosis through the upregulation of CASP9	[23]
hsa-miR-200b-5p	Suppresses the epithelial-mesenchymal transition	[24]
hsa-miR-27b-3p	Directly targets and inhibits the expression of nuclear receptor subfamily 5 group A member 2 (NR5A2) and cAMP-response element binding protein 1 (CREB1) and regulates ESR1, PGR1, FOXM1 and 14-3-3 family genes	[25, 26] [27]
hsa-miR-29a-3p	Suppresses proliferation of tamoxifen-resistant breast cancer cells	[28]
hsa-miR-503-5p	Suppresses proliferation by regulating the oncogene ZNF217	[29]

and sequencing was done by ZAO Genoanalytica (Moscow, Russia) as follow: microRNA was extracted from by PureLink RNA Micro Kit (#12183-016) according to manual. Library preparation was carried out with NEBNext® Small RNA Library Prep Set for Illumina® (E7330S) according to manual. More than 2500 miRNAs were identified in the exosomal samples. The comparison of miRNA profile of MCF-7 and MCF-7/T exosomes revealed 877 miRNA differentially expressed in MCF-7/T exosomes, among them 459 miRNA were up-regulated, and 418 miRNA were down-regulated. Study of miRNA of MCF-7/M exosomes showed 751 differentially expressed miRNA including 388 up-regulated and 363 down-regulated miRNAs. The comparative analysis of the miRNA differentially expressed in the both MCF-7/T and MCF-7/M resistant exosomes revealed 180 up-regulated and 202 down-regulated miRNAs (Table 1).

The following bioinformatical analysis of the common differentially expressed miRNAs revealed 4 up-regulated and 8 down-regulated miRNAs associated with progression of hormonal resistance of breast tumors. Importantly, we revealed the strong correlation between change vector of miRNA expression in the resistant exosomes and type of miRNA activity. Namely, all of 4 up-regulated miRNAs were described

as resistance-associated mitogenic factors, whereas 8 down-regulated miRNAs were considered as the pro-apoptotic or hormone-sensitive- associated factors (Table 2).

As mentioned above, the parent cells response to the resistant exosomes involves the activation of Akt – one of the key signaling supporting the growth of the hormone-resistant cells [30]. The key role of the Akt signaling in the transferring of the resistant phenotype was substantiated in our experiments, showing the full block of the exosome-induced resistance of MCF-7 cells in the presence of PI3K inhibitor wortmannin [11]. Here, the analysis of 4 resistance-associated exosomal miRNAs revealed 2 miRNAs, mir-101, mir-181b, which up-regulated PI3K signaling. Both of miRNAs exert their effect via the suppression of PTEN phosphatase which is main physiological antagonist of PI3K [16].

Totally, we demonstrated the unique protein and miRNA composition of the exosomes of the resistant cells, identified the possible intercellular targets of exosomes and revealed the key exosomal miRNAs associated with hormonal resistance. Further studies are required to explore the role of the each of the identified miRNAs in the progression of the exosome-induced hormonal resistance.

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Conflict of interest

The authors declare that they have no conflict of interest.

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