ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2018, Vol. 44, No. 2, pp. 129–139. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © N.A. Logvina, V.O. Shender, G.P. Arapidi, T.D. Holina, 2018, published in Bioorganicheskaya Khimiya, 2018, Vol. 44, No. 2, pp. 113–125.

REVIEW ARTICLE

A Role of Vesicular Transduction of Intercellular Signals in Cancer Development

N. A. Logvina[1], V. O. Shender, G. P. Arapidi, and T. D. Holina

Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow GSP-7, 117997 Russia

Received November 25, 2016; in final form, August 23, 2017

Abstract—Export of biologically active compounds is essential for any living cell. Transport of bioactive molecules through a cellular membrane can be active, or passive, or vesicular. In the past decade, vesicular transduction of intercellular signals has attracted great interest in the scientific community. An extremely important role of the vesicle transduction has been established for almost all processes in a living body. Not only profiles of protein and RNA expression in a cell, but also its secretome change during various pathologies, including cancer development. The enhanced secretion of vesicles by transformed cells is one important factor in creating a special microenvironment that favors tumor progression. At present, a role of exosomes has been demonstrated for such important processes as an epithelial-mesenchymal transition, angiogenesis, metastatic niche formation, chemotherapeutic resistance, and interaction with the immune system. The special biological role of the extracellular vesicles and their basic differences depend on their molecular composition. Therefore, special protein and lipid markers are responsible for a vesicular targeted delivery with information due to the preferable interaction with cells of a definite type. The exosomes of cancer cells can facilitate apoptosis or growth of neighboring malignant cells depending on the exosome composition. These and other special features of the extracellular vesicles make studies of their composition and role especially interesting and attract significant attention from researchers. Despite the rapid progress in this field, there are still many unresolved problems, such as a search for specific markers which allow identification of different types of vesicles or vesicles secreted by distinct cells, as well as screening of vesicular markers of cancers and other diseases that are associated with disorders in a functioning immune system. This review is mainly focused on the role of intercellular vesicular transport of bioorganic molecules in cancer progression. We believe that a successful treatment of oncological diseases is impossible without an understanding of the intercellular communication of both cancer cells between each other and with other systems of an organism and with a concept of an active participation of the cell-secreted vesicles in this process.

Keywords: transduction of intercellular signals, exosomes, extracellular vesicles, cancers

DOI: 10.1134/S1068162018010120

INTRODUCTION

In multicellular organisms, signals are transduced between cells not only via a direct contact of two cells, but with the use of cell-secreted molecules, including nucleic acids, lipids, short peptides, proteins, low-molecular-weight organic compounds, and other substances. An interaction of these secreted molecules with other cells can change the state of the latter, and

[1] Corresponding author: e-mail: logvinata@gmail.com.

Abbreviations: ABs, apoptotic bodies; EV, an extracellular vesicle; MVBs, multivesicular bodies; ADAM10, the disintegrin and metalloproteinase domain 10; AKT, the alpha serine/threonine-protein kinase; Bcl-2, the B-cell lymphoma 2; Bim, the Bcl-2-like protein 11; BIRC5, the baculoviral inhibitor of apoptosis repeat-containing 5; Bsx, the brain-specific homeobox protein homolog; CXCR2, the C-X-C chemokine receptor type 2; CD, a cluster of differentiation; EDH1, the EH domain-containing protein 1, where EH is the EPS15 homologue and EPS15 is the epidermal growth factor receptor substrate 15; EGF, the epidermal growth factor; EGFR, the receptor of the epidermal growth factor; ESCRT, the endosomal sorting complex required for transport; EMMPRIN, the extracellular matrix metalloproteinase inducer; EpCAM, an epithelial cell adhesion molecule; EPS8L, the epidermal growth factor receptor kinase substrate 8-like protein 2; ERG, the ETS-related gene, ETS, erythroblast transformation-specific; ERK, extracellular signal–regulated kinases; GPC1, glypican 1; HER-2, the human epidermal growth factor receptor 2; HSP, heat shock proteins; IL, interleukin; JNK, the c-Jun *N*-terminal kinase; L1CAM, the L1 cell adhesion molecule; MAPK, the mitogen-activated protein kinase; MHC, the major histocompatibility complex; miR, a micro-RNA; MLCK, the myosin light-chain kinase; NFκB, the nuclear factor kappa-light-chain-enhancer of activated B cells; PCA, a prostate cancer antigen; PDCD4, the programmed cell death protein 4; PI3, phosphoinositide 3-kinase; PLD, phospholipase D; PTEN, phosphatase and tensin homolog deleted on chromosome 10; Rab, the Ras-related protein in brain; Ras, the rat sarcoma; Rho, the ρ Greek letter; ROCK1, the rho-associated, coiled-coil-containing protein kinase 1; Src, sarcoma; TGF, the transforming growth factor; TMPRSS, the transmembrane serine protease 2; TSG101, the tumor susceptibility gene 101; TYRP-2, the tyrosinase-related protein 2; VEGF, the vascular endothelial growth factor; Vps4, the vacuolar protein sorting-associated protein 4.

Table 1. Adapted from [4]

Characteristics	Exosomes	Ectosomes	Apoptotic bodies
Size, nm	30–150	100–1000	50–5000
Biogenesis	MVBs	Plasma membrane	Fragmentation and disassembling of the cell components
Density	1.10–1.14 g/mL	1.12–1.20 g/mL	Not determined
Enrichment with proteins	ESCRT Signal molecules Oncogenes Integrins Receptors	Enzymes Mitochondrial proteins Ribosomal proteins Centrosomal proteins	Cytoplasmic proteins Proteins of the endoplasmic reticulum Proteins of the Golgi apparatus

the spectrum of possible reactions is very wide, from the activation of proliferation and differentiation to the induction of apoptosis. Various cell-secreted vesicles participate in the formation of an extracellular medium. Exosomes are the most-studied vesicles. Extracellular vesicles (EVs) contain many proteins, lipids, and nucleic acids. The vesicles can also influence recipient cells by a more complex way than separate secreted molecules owing to a more complex composition of the vesicles and a higher local concentration of the vesicular components.

Although EVs were first identified even in 40s of the twentieth century [1], they have been considered as something specific for definite organs or as "residues" of dead cells for a long time. At present, EV existence has been demonstrated for all types of cells and for all three domains of the life tree: bacteria [2], archaea [3], and eukaryotes [1].

Types of extracellular vesicles. Nowadays, the classification of EVs is based on their biogenesis. Three fundamentally different ways of vesicle formation give rise to three vesicle types: exosomes, ectosomes (or microvesicles), and apoptotic bodies (Table 1) [4–6].

Exosomes are small vesicles whith sizes of 40–100 nm and a density of 1.10–1.14 g/mL (see Table 1) [6]. They are secreted by cells of different tissues. Exosomes were found in different biological tissues (urine, milk, blood, and cancer ascites) [7]. Exosomes are formed as a result of a fusion of a multivesicular endosome that contains intraluminal vesicles (future exosomes) with a plasma membrane. The multivesicular endosomes can conjugate with a cellular plasmic membrane with a subsequent release of exosomes, but they can also use their content for a degradation by a fusion with lysosomes. At present, a future of a concrete fusion product can not be exactly predicted.

Four endosomal complexes (ESCRT, Endosomal Sorting Complex Required for Transport 0–III) and the associated proteins (for example, Vps4 and Alix) are responsible for the formation of the intraluminal vesicles. ESCRT 0, I, and II recognize and bind ubiquitinylated proteins on a surface of an endosome, whereas ESCRT III forms and cleaves the vesicles. During the exosome formation, ESCRT and the associated proteins can recognize and pack nonubiquitinylated proteins which are the exosome "load" [6]. The tetraspanin transmembrane proteins which are actively involved in the exosome membranes also actively participate in the protein sorting for the exosomes [8, 9].

Both the basic ESCRT-mediated and the ESCRT-independent ways of the exosome formation exist [10]. The latter requires the presence of lipid islets (rafts) in a membrane where sphingomyelinase converts sphingomyelin into ceramide [11], which facilitates the vesicle formation. In this case, a fusion of a malty-vesicular endosome with a plasma membrane (PM) and the exosome release occur with the participation of small Rab-GTP-ases. RAB27B participates in the binding of the endosome with the actin cortex, whereas RAB27A favors the endosome fusion with PM [12].

The exosomes can be specifically recognized by target cells. The adhesion molecules, in particular integrins, are responsible for the key stage of this recognition. The exosomes can affect a cell in several ways after the cell contact. They can stay outside the cell, and binding to a cellular receptor will induce a signal cascade in this case. The exosomes can also be fused with a cellular membrane and release their content inside the cell, or they can be absorbed during endocytosis. In this case, the absorbed exosome can be transported in lysosomes for its degradation or can be fused with the endosome membrane and release the content in the cytoplasm [6].

In distinction to the exosomes, ectosomes (microvesicles) have a size of 100–1000 nm, are gathered near a plasma membrane, and released by a protrusion of the membrane and splitting off. Cancer cells often produce the so-called oncosomes that are large vesicles of size from 1 to 100 μm. The oncosomes are possibly formed by the same mechanism as the classic ectosomes [4].

Ectosome formation on a plasma membrane primarily involves a rearrangement of the membrane components and cytoskeleton and attraction of the proteins that participate in the separation of a mem-

brane fragment. This process seems simple, but is, in fact, rather complex. The first stage of the process is nucleation (the formation of special domains of grouped transmembrane proteins and lipids). Tetraspanins presumably are among the sorting proteins. A release of calcium ions occurs simultaneously with the nucleation, and a process of local damage to the cytoskeleton begins. Special translocases (flippase, scramblase, and others) increase the phosphatidylserine content on an outer side of the membrane and, thus, misbalance the structure of the lipid bilayer [13, 14]. The splitting off from the plasma membrane occurs owing to the PLD/ERK activation and phosphorylation of the MLCK kinase [15], or is due to the TSG101-induced translocation of the ESCRT-III complex and separation of the membrane fragment involving Vps4.

The third and the least-studied type of the cell-secreted vesicles are the apoptotic bodies (ABs). According to their name, ABs form in the course of apoptosis or the programmed cell death. Until now, ABs have been considered to be only a side product of cell death. However, recent data points to the fact that a set of the AB-involved factors is not random, but is strictly controlled during the ABs formation [1]. The AB sizes vary from 50 to 5000 nm, and ABs can contain organelles. In the course of apoptosis, the cytoskeleton is disassembled and protrusions (membrane vesicles), which are considered to be the AB precursors, appear [16]. The corresponding local rearrangements of the membrane components have been shown to be caused by an activation of the ROCK1 kinase and a polymerization of actin [17–19]. The ROCK1 activation occurs without the participation of the Rho GTP-ase canonical activator by a cleavage of the protein by caspase 3 [19]. During the AB formation, the outer side of the membrane is enriched by phosphatidylserine similarly to the process of the ectosome formation, and this event serves as a signal to the beginning of a phagocytosis of the dying cell [4]. However, unlike the ectosome formation, the phosphatidylserine is externalized through a Ca-independent pathway and due to the large size of the vesicle, the membrane tension is sufficient to cleave the vesicle [4, 20].

A new mechanism of AB formation was discovered in 2015. The authors called it "beads-on-a-string," because the forming structures (apoptodies) looked like long filaments from vesicles of a membrane of a dying cell. This effect was initially observed for T-lymphocytes after the action of the PANX1 pannexin inhibitor [21]. The same action was later described for approximately 45% of the apoptotic monocytes without the action of additional preparations. An investigation of AB formation during apoptosis revealed two separately regulated stages of the fragmentation of a cellular membrane in the course of apoptosis: the formation of (1) the membrane vesicles and (2) apoptodies. The apoptodies could take the "beads-on-a-string" shape under definite conditions, probably facilitating a sorting of the proteins that would be involved in the apoptotic bodies.

Bioorganic molecules in the microvesicles. The biological role and physicochemical properties of the extracellular vesicles are generally determined by their molecular composition. The vesicles of different types which are formed from the same cells are distinguished by both the membrane composition and transported molecules despite the common ancestry. At the same time, only several proteins that are unique for vesicles of one type are presently known. In other cases, we are dealing only with a comparable enrichment with concrete proteins, lipids, or RNA.

The molecular composition of exosomes. Exosomes, like other vesicles, transport intracellular proteins, nucleic acids, and peptides which are surrounded by a bilayer lipid membrane that protects them from the extracellular medium and dilution [4, 22]. First, proteins of the cytoplasm of a donor cell are involved in the exosomes. At the same time, the composition of the exosome membranes differs from that of a membrane of the parent-cell [23]. The exosome biogenesis involves the endosomes and the formation of multivesicular bodies (MVBs), and the exosome membrane is enriched by the proteins which are responsible for the MVB formation and the membrane fusion. Thus, the exosomes are enriched by annexins, flotilins, GTP-ases, integrins, tetraspanins, and many other proteins. It is interesting that antigen-presenting proteins (the MHC I and II complexes) are often found in the exosomes independently of cell type [7, 24–26]. Specific protein patterns that correspond to the exosomes of different cells or tissues have been identified along with proteins common for all the exosomes [7]. It is still unknown how these proteins penetrate the exosomes and how accidental is their presence in the vesicles.

The exosomes are enriched with specific lipids (ceramides, cholesterol, phosphatidylserine, sphingolipids, and others) along with the proteins. The exosome membranes do not contain lysobiphosphatidic acid (LBPA) even though it has been found in the endosomes and the MVB internal vesicles and is considered to be necessary for their formation [27–30]. It is explained by the proposal [28] that LBPA is exceptionally important for the formation of MVBs which are further involved in lysosomes and do not participate in the exosome formation. The difference in lipid composition of MVBs which are further included in various biological processes can result from the strict control over the MVB formation and subsequent fate, contradicting the more widespread opinion of the random distribution of components between the different MVB types [25]. Another special feature of the exosome membrane is the presence of lipid rafts. The lipid rafts are detergent-stable membrane fragments which are enriched by cholesterol and sphingolipids and saturated by phospholipids. Several proteins, for exam-

Table 2. Exosomal markers of cancers (modified on the basis of [26, 38])

Cancer	Exosomal markers	References
Melanoma	CD69, CD63, HSP70, HSP90, TYRP-2, very late antigen-4 (VLA-4), α4β1-integrin, CD49d/CD29	[36, 40]
Glioblastoma	EGFRvIII, angiogenin, IL-8, VEGF	[37, 41]
The prostate cancer	BIRC5, PCA, PCA3,	[42]
The ovarian carcinoma	L1CAM, CD24, ADAM10, EMMPRIN, claudin	[43, 44]
The cancer of the urinary bladder	Resistin, N-RAS GTP-ase, EPS8L2, EPS8L1, alpha-subunit of the guanine-binding protein of group S, the retinoic-acid-induced protein 3, the halectin-3-binding protein, EDH1	
The pancreatic cancer	GPC1	[45]
The intestinal cancer	EpCAM, cadherin-17, mucin 13 (MUC-13), keratin 18, claudins, ephrin B1	[7]

ple, flotilins, are accumulated in the same membrane regions [25].

It is also believed that the exosomes have a characteristic polysaccharide and glycan pattern (signature) on the outer side of the membrane. Mannose, α-2,3-sialic acids, α-2,6-sialic acids, complex glycans, and polylactosamines are the basis of this pattern [31, 32].

RNA is an important component of the exosomes and other vesicles. Exosomal transport of matrix, micro, and several noncoding RNA has been demonstrated [33]. In addition, exosomal transport of fragments of the double-stranded DNA has been described in separate reports. A possible biological role of this DNA and its involvement in the exosomes have still not been elucidated [34].

The presence of components specific for parent-cells in the exosomes provides their use as biomarkers of diseases. The exosomal biomarkers are more specific and stable in comparison with other biomarkers which are identified in blood, urine, and other biological tissues, and, therefore, these markers are of interest for the diagnostics. Many exosomal components (proteins, micro-RNA, and lipids) have been proposed as the markers, but additional studies are necessary for their real application to clinical practice [23].

Cancer cells are known to secrete considerably more vesicles than normal cells; therefore, cancers become one of the main directions of the search for exosomal markers (Table 2) [23, 35]. For example, tetraspanins can be used for diagnostics of oncological and infectious diseases [23]. Secretion of the $CD63^+$ exosomes increases during melanoma [36] and several other cancers [23], and CD63 is proposed as one of the oncomarkers. Several exosomal proteins can be applied to the diagnostics of the brain cancers and other pathologies of the central nervous system. Variation III of the epidermal growth factor (EGFRvIII) is a specific marker of glioblastoma [37]. EGFR, EGFRvIII, and TGFβ have been also found in the exosomes which are isolated from the blood serum of patients with various brain cancers [38]. Moreover, the results point to a possible role of the exosomes in the immune response and pathogenesis during cancers and neurodegenerative diseases. The exosomes with the characteristic protein aggregates have been found in the cerebrospinal fluid of patients suffering from Alzheimer's disease, Parkinson's disease, and Creutzfeldt–Jakob syndrome [39].

Many exosomal markers have been identified during studies of the exosomes that were isolated from urine. The urinal exosomes are assumed to indicate diseases of the urogenital system, including cancers. The content of eight proteins (the alpha-subunit of the guanine-binding protein of the S group, the retinoic-acid-induced protein 3, resistin, and five proteins associated with the EGFR activation) has been shown to be increased in the urinal exosomes during the cancer of the urinary bladder. Two other urinal exosomal proteins (PCA-3 and TMPRSS2:ERG) have been proposed as the markers for prostate cancer [42].

The alpha-1 antitrypsin and the H2B1K histone have been identified as specific markers for urothelial carcinoma [23, 46]. The urinal exosomes can be used for diagnostics of both urogenital diseases and intestinal cancer. The exosomal EpCAM proteins, kadgerin-17, mucin 13 (MUC-13), keratin 18, claudins, and ephrin B1 are specific markers for this cancer [7]. The exosomes that contain the surface GPC-1 proteoglycan have been proposed for the diagnostics of the intestinal cancer. Moreover, the GPC-1 level has been shown to correlate with the life-time of the patients [45].

Along with proteins, the exosomes contain RNAs which can also be used for diagnostics of oncological diseases (Table 3) [23]. Researchers pay special attention to micro-RNAs, although long noncoding RNAs and matrix RNAs are also involved in the exosomes. The micro-RNAs are short (19–25 nucleotides) noncoding RNAs wich are able to specifically regulate expression of target genes. In most cases, the micro-RNAs are present in the exosomes as a precursor [47, 48], and the major part of the micro-RNAs in the serum and saliva is located inside the exosomes [49]. RNA is assumed to be more stable and biologically

Table 3. Exosomal micro-RNA markers [26]

Exosomal micro-RNAs	Cancers	References
miR-21, -141, -200a, -200b, -200c, -203, -205, -214	Ovarian carcinoma	[51]
miR-17, -3p, -21, -20b, -223, -301, let-7f	Lung cancer	[52, 53]
miR-141, miR-375	Prostate cancer	[54, 55]
miR-21, miR-1246	Esophageal carcinoma (SCC)	[56, 57]
miR-21	Breast cancer	[58]
Let-7 family miRNAs	Stomach cancer	[59]

active in the exosomes than RNA that is present in the extracellular medium as an RNA-protein complex [50]. The micro-RNAs have been repeatedly proposed as markers for various diseases.

Molecular composition of the ectosomes and the apoptotic bodies. The size and composition of the ectosomes are more heterogeneous than those of the exosomes. The ectosomal membranes differ from those of the parent-cell similarly to the exosomal membranes. However, in the case of the ectosomes, the specific differences result from peculiarities of the processes of nucleation and blastogenesis. In general, the ectosomes transport the same types of bioorganic molecules as the exosomes, but the composition of the ectosomes is much less studied. Such proteins as matrix metalloproteinases, glycoproteins (GPIb, GPIIb-IIIa, P-selectin, and others) [60–62], integrins [62, 63], EGFR [41], and the cytoskeletal components [64] (for example, β-actin and α-actinin-4) are involved in the ectosomes.

It should be taken into consideration that the ectosomal composition of the same cell type can be dramatically changed with variation of environmental conditions. Proteomic analysis demonstrated that the content of the major part of ectosomal proteins changes under the action of different stimuli on monocytes. However, a small group of proteins (approximately 100 proteins, including the cytoskeletal components, receptors of the cellular adhesion, signal molecules, and mitochondrial proteins) is always present [64]. The proteomic analysis also demonstrates an enrichment of the ectosomes with mitochondrial, ribosomal, and centrosomal proteins in comparison with the exosomes [65]. Fewer tetraspanins, proteins of the ESCRT complex and other proteins have been found to participate in the exosome biogenesis in comparison with the exosomes [65]. Oncogenic ectosomes (oncosomes) are enriched with mitochondrial proteins [66]. Recently, the uniqueness of the ectosome-transported RNAs has been also shown [67].

The lipid composition of the ectosomal membranes also differs from that of a plasma membrane. The ectosomes contain more phosphatidylserine, which participates in their biogenesis, phosphatidyl choline, sphingomyelin, and phosphatidylethanolamine [68]. A lipidome analysis that involves a determination of acyl residues of fatty acids has demonstrated the wide variety of ectosomal lipid composition [69].

The absence of universal terms for different types of vesicles complicates further the analysis of factors specific for the ectosomes and other vesicles. As a result, different investigators have named the exosomes, the ectosomes, and the apoptotic bodies as microvesicles, nanovesicles, oncosomes, membrane vesicles, microparticles, etc. at different times. The exosome determination is relatively simple according to their size, and the term "exosome" is more often used. However, the literature data on the exosomes should be interpreted very carefully [4].

The apoptotic bodies have been considered to be cellular "garbage" for a long time, and they have been studied even less than the ectosomes. The apoptotic bodies of lymphocytes and monocytes in atherosclerotic plaques were found to be enriched with phosphatidylserine, coagulation factor III, and annexin A5 [70]. The later proteomic investigation of ABs of the mouse thymocytes revealed 142 differentially expressed proteins, including the heat shock proteins, histone-associated proteins, cytoplasmic proteins, pseudooncogens, and the proteins that influenced functioning of the immune system [71].

Eleven specific proteins, such as annexin A5, the β6 heat shock protein, protein-1 that was associated with a receptor of the low-density lipoproteins, and RAB11A were determined by a proteomic analysis of ABs of epithelial cells of the human bile ducts [72]. Most of the identified proteins were involved in such signal pathways as an activation of the NF-κB factor, ERK, and Notch, as well as signal cascades with participation of IL8 and CXCR2.

A comparable proteomic analysis of ABs and the cells subjected to the apoptosis was recently performed [73]. As a result, a difference in the occurrence was found for 1028 proteins. Significantly low content of nuclear components of a cell in ABs was of particular interest. The authors believed that this fact was evidence for the nonrandom occurrence of separate proteins in ABs and the possible existence of protein sorting during the AB formation.

Creation of special microenvironment by cancer cells. Cancer is not a simple large mass of transformed cells, but a complex cellular conglomerate which can override the functioning of surrounding cells. A multiple network of interactions between cancer and normal cells creates a special microenvironment in which untransformed cells often facilitate the cancer development in different states of carcinogenesis. An interaction between various cells is coordinated by a complex network that involves an exchange of extracellular vesicles [74]. The main role in regulation of the microenvironment which is created by cancer cells has been historically ascribed to low-molecular-weight compounds, cytokines, and growth factors. In recent years, more attention has been paid to a vesicular transduction of intercellular signals. The role of EVs in regulation of a complex of the interrelated processes of the cancer appearance and development is simultaneously increased [25].

Transduction of signals of proliferation of malignant cells and resistance to the signals of inhibition of cellular growth. The exosomes of the cancer cells participate in transduction of the proliferation stimuli. The exosomes were shown to be able to transfer the proliferative signals from donor to acceptor cells during breast cancer [75], glioblastoma [37], and colorectal cancer [76, 77]. Active transformed cells usually support a capability of permanent division through activation of the PI3K/AKT or MAPK/ERK signal pathways. In some cases, the exosomes also take part in the activation of one or both pathways [78]. However, this is not the only proliferation possibility. The exosomes of hepatocellular carcinoma change the expression level of the TGFβ growth factor [79]. Receptors of tyrosine kinases [80], oncogenes [76], phosphoproteins [77], matrix RNAs and micro-RNAs [76, 77, 81] are among the exosomal molecules that can transduce the proliferative signals. Not only the cancer cells, but macrophages, mesenchymal stem cells of the bone marrow, mast cells and other cells can give analogous signals [50].

A considerable part of anticancer therapy is aimed at metastasis treatment. The exosomes of the cancer cells play an important role in the appearance of metastases [50]. In particular, the cells of colorectal cancer release exosomes that are enriched with mRNAs of the cell-cycle proteins and, thus, facilitate an active division and metastasis of the cancer cells. It has been recently demonstrated that the exosomes actively participate in the creation of the so-called metastasis niche, and a selective uptake of the exosomes by definite cells determines where the metastasis appears. Integrins which are located on the exosomal surface and determine the uptake selectivity and activation of the Src-dependent signal pathway and the S100 protein play an important role in this process [82].

The exosomes of intestinal cancer change the phenotype of cells of the smooth muscles via activation of metalloproteinases and prepare a medium for the metastasis [83]. The exosomes that are released by the melanoma cells increase their migration capability and make the cells of the lymph nodes ready for the metastasis [84]. The exosomes of the pancreas have been shown to form a niche for the metastasis in the liver [85]. Absorption of the cancer exosomes has caused the TGFβ secretion by the Kupffer cells and an enhancement of the fibronectin expression by the stellate cells. These events have attracted macrophages and granulocytes in the liver and facilitated the formation of a niche for the metastasis. This process has still not been studied in detail, but the macrophage migration inhibitory factor (MIF), that is actively transported by the exosomes of the pancreatic cancer, is assumed to play the key role [85].

The role of the exosomes in resistance to the signals which inhibit the cell growth is poorly investigated. It is presumed that the exosomes of cancer cells decrease the action of the suppressors through a transfer of transcripts of the H-Ras and N-Ras oncogenic factors and the Rab proteins [86, 87]. In addition, the oncosuppressors can be exported by the exosomes from a cell. For example, the PTEN protein, which is known to decrease the cancer growth, is exported by the exosomes, preserves its activity out of a cell, and can additionally inhibit the growth of cancer-surrounding cells [50, 81].

Overcoming apoptosis. Apoptosis is programmed cell death, which is one of the necessary daily processes for survival of the organism. However, an abrogation of triggering of the apoptosis program in the transformed cells is necessary for the appearance and development of a cancer. The exosomes of the cancer cells can increase both the direct and indirect ability of the tumor to overcome apoptosis.

Most of the recent papers point to a direct participation of the exosomes in the inhibition of apoptosis. However, the exosomes play the role of an activator of cell death in several cases. For example, the exosomes of the cells of the pancreatic cancer induce the mitochondrial pathway for apoptosis development [88] through an increase in the expression of the Bax proapoptotic factor and a decrease in the expression of the Bcl-2 antiapoptotic factor.

Nevertheless, the exosomes most often exhibit the antiapoptotic effect on the cancer cells and promote the development of aggressive metastasizing cancers which are frequently resistant to therapy. The exosomes of cancers of the stomach and urinary bladder inhibit the apoptosis of the corresponding transformed cells via enhancement of the expression of Bcl-2 and cycline-D1 and decrease in the expression of Bax and caspase-3 [89, 90]. The exosomes from patients with ovarian carcinoma contain large amounts of the miR-21 micro-RNA, which is known to control functioning of the PDCD4 proapoptotic factor. The level of this protein in the cells of many cancers is known to

negatively correlate with the miR-21 level. The exact mechanism of this regulation is still not known, but we can propose a similar action for the exosomal miR-21 [51, 91].

The DNA damage and chromosome instability result in activation of the p53 protein in many cancer cells. This activation induces the apoptosis and an active export of proapoptotic factors, including those in the exosomes [81]. The mutant forms of the inactive p53 have been recently shown to be transmitted by the exosomes to neighboring cells, and this process can result in an extension of the mutant form [34, 92].

The exosomes that facilitate the inhibition of cellular death can be produced not only by the malignant cells of cancers, but their microenvironment as well. For example, the exosomes of the stromal cells of the bone marrow inhibit the JNK-dependent signal pathway and the expression and phosphorylation of the Bim proapoptotic factor during multiple myeloma of the plasma cells in the bone marrow [93].

Development of resistance to chemotherapy. The exosomes that are released by malignant cells can also protect the cells from the action of anticancer agents. The simplest way for this protection is the exosomal export of significant amounts of the agent from the cell. It is anticipated that the cisplatin-treated melanoma cells decrease the cisplatin efficacy in precisely this way [94]. The exosomes of the cisplatin-resistant cells of the ovarian carcinoma are shown to contain 2.6 times more cisplatin than those of the therapeutically sensitive cells. This fact can probably explain the decreased platinum concentration inside the cancer cells [95]. Similarly, the doxorubicine-treated cells released this therapeutic agent in microvesicles, and the level of the vesicle release correlated with the resistance to doxorubicine [96]. The exosomes of the cells of breast cancer with an enhanced expression of HER-2 act as a trap after the treatment with trastusumab, increasing the resistance of the parent-cells to this agent and its necessary dose [97]. The exosomes of the B-cellular lymphoma have the analogous effect on the treatment with rituximab, which is an antibody to the CD20 protein. The release of the exosomes with the increased content of CD20 can considerably decrease the amount of the antibodies that react with the target cells. For example, approximately half of the antibodies were associated with the exosomes three hours after the rituximab administration [98].

The exosomes can increase resistance to the chemotherapy by transport of vitally important factors and activation of the corresponding signal cascades along with the decrease in the efficacy of an anticancer agent due to the reduction of its quantity inside a cell.

The exosomes of the cisplatin-treated cells of lung cancer increase the cisplatin resistance of other cells which are not subjected to a preliminary treatment with this medicine [99]. Scientists associate this fact with a considerable change in the amount of the exosomal matrix and micro-RNAs that are associated with the cisplatin resistance after the treatment of the cells with cisplatin. The same phenomenon has been observed for the doxitaxel-treated cells of prostate cancer and has been explained by the action of miR-34 [100, 101]. The exosomal transport of micro-RNA also enhances the resistance of neuroblastoma to chemotherapy [102]. The GW4869 inhibitor of the exosome release restores the sensitivity of the neuroblastoma cells to cisplatin. Other resistance factors that increase a resistivity of acceptor cells are involved in the exosomes along with micro-RNA, which attracts attention of researchers. The exosomes of the cells of the hepatocellular carcinoma contain the ROR long noncoding RNA that is able to decrease the level of cell death through the TGF-dependent pathway [103]. The exosomes that increase the resistance to therapy can be produced not only by the malignant cells themselves, but by the microenvironmental cells (for example, by the tumor-associated fibroblasts) as well [104].

Neoangiogenesis. One of the problems of cancer development is hypoxia. Here, the cancer begins to release to the environment factors which promote metastasis and angiogenesis. The hypoxia increases the level of the exosome release by the transformed cells [105]. The hypoxia-inducible factors (HIF) have been shown to participate in this process [106]. The enhancement of the exosome secretion by the cells of breast cancer presumably changes the cancer microenvironment and facilitates vascular growth via activation of the epidermal growth factor (EGF) in the endothelial cells [107]. The glioblastoma cells secrete the exosomes which can change the phenotype of the endothelial cells in vitro and promote vascular growth in vitro [108]. The hypoxia-resistant cells of the multiple myeloma release the exosomes with the significantly increased content of the miR-135b micro-RNA which can also induce the active vascular growth [50, 106].

CONCLUSIONS

A complex understanding of processes, including interactions between various components both inside and outside a cancer, is necessary for a successful and complete treatment of a malignant tumor. In the recent decade, a realization of the importance of exosomes and other EVs in the intercellular interaction has dramatically increased. The EV role in the interaction of the spatially distant cells is being progressively elucidated, as well as their influence on the development of cancers. EVs can transport virions, RNAs, proteins and their complexes, and, even, double-stranded DNAs of living cells. It is assumed that EVs can promote development of cancer resistance to chemotherapy and an enhancement of the capability for metastasis and invasiveness. However, EV influence on the formation of the cancer-specific microenvironment that involved a variety of cell types is still not completely understood. In this review, we focused on

the EV role in cancer progression, but EVs participate in many processes in a healthy organism. The exosomes and other EVs are secreted by neurons, epithelial and stem cells, and the cells specific for different organs and the immune system. The range of their effects on an organism is tremendously wide. For example, the exosomes of the stem cells favor healing of the cardiac muscle, whereas the exosomes of the nerve cells actively participate in the formation of the medullary sheath by Schwann's cells. The vesicular transport of prions, beta-amyloid peptides, synucleins, and other compounds is responsible for the development of several neurodegenerative diseases. In general, EVs allow a transition between subcellular and organ-tissue levels of organization of living matter. EVs provide an influence on the processes inside one cell on the functioning of other cells and organs with which this cell is not directly contacted. The specific absorption of vesicles by the cells of a definite type make the transduction of complex signals, which is simultaneously controlled by several factors, to be directed and relatively selective.

Undoubtedly, many novel EV functions will be discovered soon. The absence of methods for an effective fractionation and comparison of various types of vesicles is one of obstacles to further studies of EVs. Active EV investigation has begun relatively recently, and the standard methods for isolation, characterization, and determination of EVs have not yet been created. The facts that have been described in this review point to the important role of the exosomes and its difference from that of the endosomes and the apoptotic bodies and demonstrates the particular importance of the development of these methods and the separate investigation of different types of vesicles.

ACKNOWLEDGMENTS

This study was supported by the Russian Scientific Foundation, project no. 14-50-00131.

REFERENCES

1. Chargaff, E. and West, R., *J. Biol. Chem*., 1946, vol. 166, pp. 189–197.
2. Knox, K.W., Vesk, M., and Work, E., *J. Bacteriol.*, 1966, vol. 92, pp. 1206–1217.
3. Soler, N., Marguet, E., Verbavatz, J.-M., and Forterre, P., *Res. Microbiol.*, 2008, vol. 159, pp. 390–399.
4. Kalra, H., Drummen, G.P.C., and Mathivanan, S., *Int. J. Mol. Sci.*, 2016, vol. 17, p. 170.
5. Bobrie, A., Colombo, M., Raposo, G., and Thery, C., *Traffic*, 2011, vol. 12, pp. 1659–1668.
6. Raposo, G. and Stoorvogel, W., *J. Cell Biol.*, 2013, vol. 200, pp. 373–383.
7. Mathivanan, S., Lim, J.W.E., Tauro, B.J., Ji, H., Moritz, R.L., and Simpson, R.J., *Mol. Cell Proteomics*, 2010, vol. 9, pp. 197–208.
8. Pols, M.S. and Klumperman, J., *Exp. Cell Res.*, 2009, vol. 315, pp. 1584–1592.
9. Perez-Hernandez, D., Gutierrez-Vazquez, C., Jorge, I., Lopez-Martin, S., Ursa, A., Sanchez-Madrid, F., Vazquez, J., and Yanez-Mo, M., *J. Biol. Chem.*, 2013, vol. 288, pp. 11649–11661.
10. Stuffers, S., Sem, WegnerC., Stenmark, H., and Brech, A., *Traffic*, 2009, vol. 10, pp. 925–937.
11. Trajkovic, K., Hsu, C., Chiantia, S., Rajendran, L., Wenzel, D., Wieland, F., Schwille, P., Brugger, B., and Simons, M., Science, 2008, vol. 319, pp. 1244–1247.
12. Ostrowski, M., Carmo, N.B., Krumeich, S., Fanget, I., Raposo, G., Savina, A., Moita, C.F., Schauer, K., Hume, A.N., Freitas, R.P., Goud, B., Benaroch, P., Hacohen, N., Fukuda, M., Desnos, C., Seabra, M.C., Darchen, F., Amigorena, S., Moita, L.F., and Thery, C., *Nat. Cell Biol.*, 2010, vol. 12, pp. 19–30.
13. Bevers, E.M. and Williamson, P.L., *FEBS Lett.*, 2010, vol. 584, pp. 2724–2730.
14. Daleke, D.L., *J. Lipid Res.*, 2003, vol. 44, pp. 233–242.
15. Muralidharan-Chari, V., Clancy, J., Plou, C., Romao, M., Chavrier, P., Raposo, G., and D'Souza-Schorey, C., *Curr. Biol.*, 2009, vol. 19, pp. 1875–1885.
16. Lane, J.D., Allan, V.J., and Woodman, P.G., *J. Cell Sci.*, 2005, vol. 118, pp. 4059–4071.
17. Chang, J., Xie, M., Shah, V.R., Schneider, M.D., Entman, M.L., Wei, L., and Schwartz, R.J., *Proc. Natl. Acad. Sci. U. S. A.*, 2006, vol. 103, pp. 14495–14500.
18. Sebbagh, M., Renvoize, C., Hamelin, J., Riche, N., Bertoglio, J., and Breard, J., *Nat. Cell Biol.*, 2001, vol. 3, pp. 346–352.
19. Coleman, M.L., Sahai, E.A., Yeo, M., Bosch, M., Dewar, A., and Olson, M.F., *Nat. Cell Biol.*, 2001, vol. 3, pp. 339–345.
20. Suzuki, J., Denning, D.P., Imanishi, E., Horvitz, H.R., and Nagata, S., *Science*, 2013, vol. 341, pp. 403–406.
21. Poon, I.K.H., Chiu, Y.-H., Armstrong, A.J., Kinchen, J.M., Juncadella, I.J., Bayliss, D.A., and Ravichandran, K.S., *Nature*, 2014, vol. 507, pp. 329–334.
22. Mathivanan, S., Ji, H., and Simpson, R.J., *J. Proteomics*, 2010, vol. 73, pp. 1907–1920.
23. Yakimchuk, K., *Devices Methods Measurements,* 2015, vol. 5, pp. 228–235.
24. Subra, C., Laulagnier, K., Perret, B., and Record, M., *Biochimie*, 2007, vol. 89, pp. 205–212.
25. Ciardiello, C., Cavallini, L., Spinelli, C., Yang, J., Reis-Sobreiro, M., de Candia, P., Minciacchi, V.R., and di Vizio, D., *Int. J. Mol. Sci.*, 2016, vol. 17, p. 175.
26. Lydic, T.A., Townsend, S., Adda, C.G., Collins, C., Mathivanan, S., and Reid, G.E., *Methods*, 2015, vol. 87, pp. 83–95.
27. Wubbolts, R., Leckie, R.S., Veenhuizen, P.T.M., Schwarzmann, G., Mobius, W., Hoernschemeyer, J., Slot, J.-W., Geuze, H.J., and Stoorvogel, W., *J. Biol. Chem.*, 2003, vol. 278, pp. 10963–10972.
28. Brouwers, J.F., Aalberts, M., Jansen, J.W.A., van Niel, G., Wauben, M.H., Stout, T.A.E., Helms, J.B., and Stoorvogel, W., *Proteomics*, 2013, vol. 13, pp. 1660–1666.

29. Laulagnier, K., Motta, C., Hamdi, S., Roy, S., Fauvelle, F., Pageaux, J.-F., Kobayashi, T., Salles, J.-P., Perret, B., Bonnerot, C., and Record, M., *Biochem. J.*, 2004, vol. 380, pp. 161–171.

30. Matsuo, H., Chevallier, J., Mayran, N., Le Blanc, I., Ferguson, C., Faure, J., Blanc, N.S., Matile, S., Dubochet, J., Sadoul, R., Parton, R.G., Vilbois, F., and Gruenberg, J., *Science*, 2004, vol. 303, pp. 531–534.

31. Saunderson, S.C., Dunn, A.C., Crocker, P.R., and McLellan, A.D., *Blood*, 2014, vol. 123, pp. 208–216.

32. Batista, B.S., Eng, W.S., Pilobello, K.T., Hendricks-Munoz, K.D., and Mahal, L.K., *J. Proteome Res.*, 2011, vol. 10, pp. 4624–4633.

33. Valadi, H., Ekstrom, K., Bossios, A., Sjostrand, M., Lee, J.J., and Lotvall, J.O., *Nat. Cell Biol.*, 2007, vol. 9, pp. 654–659.

34. Thakur, B.K., Zhang, H., Becker, A., Matei, I., Huang, Y., Costa-Silva, B., Zheng, Y., Hoshino, A., Brazier, H., Xiang, J., Williams, C., Rodriguez-Barrueco, R., Silva, J.M., Zhang, W., Hearn, S., Elemento, O., Paknejad, N., Manova-Todorova, K., Welte, K., Bromberg, J., Peinado, H., and Lyden, D., *Cell Res.*, 2014, vol. 24, pp. 766–769.

35. Zhang, X., Yuan, X., Shi, H., Wu, L., Qian, H., and Xu, W., *J. Hematol. Oncol.*, 2015, vol. 8, p. 83.

36. Logozzi, M., Milito, A., Lugini, L., Borghi, M., Calabro, L., Spada, M., Perdicchio, M., Marino, M.L., Federici, C., Iessi, E., Brambilla, D., Venturi, G., Lozupone, F., Santinami, M., Huber, V., Maio, M., Rivoltini, L., and Fais, S., *PLoS One*, 2009, vol. 4, e5219.

37. Skog, J., Wurdinger, T., van Rijn, S., Meijer, D.H., Gainche, L., Sena-Esteves, M., Curry, W.T., Jr., Carter, B.S., Krichevsky, A.M., and Breakefield, X.O., *Nat. Cell Biol.*, 2008, vol. 10, pp. 1470–1476.

38. Graner, M.W., Alzate, O., Dechkovskaia, A.M., Keene, J.D., Sampson, J.H., Mitchell, D.A., and Bigner, D.D., *FASEB J.*, 2009, vol. 23, pp. 1541–1557.

39. Howitt, J. and Hill, A.F., *J. Biol Chem.*, 2016, vol. 291, p. 26589–26597.

40. Peinado, H., Aleckovic, M., Lavotshkin, S., Matei, I., Costa-Silva, B., Moreno-Bueno, G., Hergueta-Redondo, M., Williams, C., Garcia-Santos, G., Ghajar, C., Nitadori-Hoshino, A., Hoffman, C., Badal, K., Garcia, B.A., Callahan, M.K., Yuan, J., Martins, V.R., Skog, J., Kaplan, R.N., Brady, M.S., Wolchok, J.D., Chapman, P.B., Kang, Y., Bromberg, J., and Lyden, D., *Nat. Med.*, 2012, vol. 18, pp. 883–891.

41. Al-Nedawi, K., Meehan, B., Micallef, J., Lhotak, V., May, L., Guha, A., and Rak, J., *Nat. Cell Biol.*, 2008, vol. 10, pp. 619–624.

42. Nilsson, J., Skog, J., Nordstrand, A., Baranov, V., Mincheva-Nilsson, L., Breakefield, X.O., and Widmark, A., *Br. J. Cancer*, 2009, vol. 100, pp. 1603–1607.

43. Li, J., Sherman-Baust, C.A., Tsai-Turton, M., Bristow, R.E., Roden, R.B., and Morin, P.J., *BMC Cancer*, 2009, vol. 9, p. 244.

44. Keller, S., Konig, A.-K., Marme, F., Runz, S., Wolterink, S., Koensgen, D., Mustea, A., Sehouli, J., and Altevogt, P., *Cancer Lett.*, 2009, vol. 278, pp. 73–81.

45. Melo, S.A., Luecke, L.B., Kahlert, C., Fernandez, A.F., Gammon, S.T., Kaye, J., LeBleu, V.S., Mittendorf, E.A., Weitz, J., Rahbari, N., Reissfelder, C., Pilarsky, C., Fraga, M.F., Piwnica-Worms, D., and Kalluri, R., *Nature*, 2015, vol. 523, pp. 177–182.

46. Lin, S.-Y., Chang, C.-H., Wu, H.-C., Lin, C.-C., Chang, K.-P., Yang, C.-R., Huang, C.-P., Hsu, W.-H., Chang, C.-T., and Chen, C.-J., *Sci Rep.*, 2016, vol. 6, p. 34446.

47. Chen, T.S., Lai, R.C., Lee, M.M., Choo, A.B.H., Lee, C.N., and Lim, S.K., *Nucleic Acids Res.*, 2010, vol. 38, pp. 215–224.

48. Turchinovich, A., Weiz, L., Langheinz, A., and Burwinkel, B., *Nucleic Acids Res.*, 2011, vol. 39, pp. 7223–7233.

49. Gallo, A., Tandon, M., Alevizos, I., and Illei, G.G., *PLoS One*, 2012, vol. 7, e30679.

50. Yu, S., Cao, H., Shen, B., and Feng, J., *Oncotarget*, 2015, vol. 6, pp. 37151–37168.

51. Taylor, D.D. and Gercel-Taylor, C., *Gynecol. Oncol.*, 2008, vol. 110, pp. 13–21.

52. Rabinowits, G., Gercel-Taylor, C., Day, J.M., Taylor, D.D., and Kloecker, G.H., *Clin. Lung Cancer*, 2009, vol. 10, pp. 42–46.

53. Silva, J., Garcia, V., Zaballos, A., Provencio, M., Lombardia, L., Almonacid, L., Garcia, J.M., Dominguez, G., Pena, C., Diaz, R., Herrera, M., Varela, A., and Bonilla, F., *Eur. Respir. J.*, 2011, vol. 37, pp. 617–623.

54. Mitchell, P.S., Parkin, R.K., Kroh, E.M., Fritz, B.R., Wyman, S.K., Pogosova-Agadjanyan, E.L., Peterson, A., Noteboom, J., O'Briant, K.C., Allen, A., Lin, D.W., Urban, N., Drescher, C.W., Knudsen, B.S., Stirewalt, D.L., Gentleman, R., Vessella, R.L., Nelson, P.S., Martin, D.B., and Tewari, M., *Proc. Natl. Acad. Sci. U. S. A.*, 2008, vol. 105, pp. 10513–10518.

55. Brase, J.C., Johannes, M., Schlomm, T., Falth, M., Haese, A., Steuber, T., Beissbarth, T., Kuner, R., and Sultmann, H., *Int. J. Cancer*, 2011, vol. 128, pp. 608–616.

56. Tanaka, Y., Kamohara, H., Kinoshita, K., Kurashige, J., Ishimoto, T., Iwatsuki, M., Watanabe, M., and Baba, H., *Cancer*, 2013, vol. 119, pp. 1159–1167.

57. Takeshita, N., Hoshino, I., Mori, M., Akutsu, Y., Hanari, N., Yoneyama, Y., Ikeda, N., Isozaki, Y., Maruyama, T., Akanuma, N., Komatsu, A., Jitsukawa, M., and Matsubara, H., *Br. J. Cancer*, 2013, vol. 108, pp. 644–652.

58. Corcoran, C., Friel, A.M., Duffy, M.J., Crown, J., and O'Driscoll, L., *Clin. Chem.*, 2011, vol. 57, pp. 18–32.

59. Ohshima, K., Inoue, K., Fujiwara, A., Hatakeyama, K., Kanto, K., Watanabe, Y., Muramatsu, K., Fukuda, Y., Ogura, S.-I., Yamaguchi, K., and Mochizuki, T., *PLoS One*, 2010, vol. 5, p. e13247.

60. Del Conde, I., Shrimpton, C.N., Thiagarajan, P., and Lopez, J.A., *Blood*, 2005, vol. 106, pp. 1604–1611.

61. Falati, S., Liu, Q., Gross, P., Merrill-Skoloff, G., Chou, J., Vandendries, E., Celi, A., Croce, K., Furie, B.C., and Furie, B., *J. Exp. Med.*, 2003, vol. 197, pp. 1585–1598.

62. Mezouar, S., Darbousset, R., Dignat-George, F., Panicot-Dubois, L., and Dubois, C., *Int. J. Cancer*, 2015, vol. 136, pp. 462–475.

63. Pluskota, E., Woody, N.M., Szpak, D., Ballantyne, C.M., Soloviev, D.A., Simon, D.I., and Plow, E.F., *Blood*, 2008, vol. 112, pp. 2327–2335.

64. Bernimoulin, M., Waters, E.K., Foy, M., Steele, B.M., Sullivan, M., Falet, H., Walsh, M.T., Barteneva, N., Geng, J.-G., Hartwig, J.H., Maguire, P.B., and Wagner, D.D., *J. Thromb. Haemost.*, 2009, vol. 7, pp. 1019–1028.

65. Keerthikumar, S., Gangoda, L., Liem, M., Fonseka, P., Atukorala, I., Ozcitti, C., Mechler, A., Adda, C.G., Ang, C.-S., and Mathivanan, S., *Oncotarget*, 2015, vol. 6, pp. 15375–15396.

66. Minciacchi, V.R., You, S., Spinelli, C., Morley, S., Zandian, M., Aspuria, P.-J., Cavallini, L., Ciardiello, C., Reis Sobreiro, M., Morello, M., Kharmate, G., Jang, S.C., Kim, D.-K., Hosseini-Beheshti, E., Tomlinson Guns, E., Gleave, M., Gho, Y.S., Mathivanan, S., Yang, W., Freeman, M.R., and Di Vizio, D., *Oncotarget*, 2015, vol. 6, pp. 11327–11341.

67. Lunavat, T.R., Cheng, L., Kim, D.-K., Bhadury, J., Jang, S.C., Lasser, C., Sharples, R.A., Lopez, M.D., Nilsson, J., Gho, Y.S., Hill, A.F., and Lotvall, J., *RNA Biol.*, 2015, vol. 12, pp. 810–823.

68. Weerheim, A.M., Kolb, A.M., Sturk, A., and Nieuwland, R., *Anal. Biochem.*, 2002, vol. 302, pp. 191–198.

69. Losito, I., Patruno, R., Conte, E., Cataldi, T.R.I., Megli, F.M., and Palmisano, F., *Anal. Chem.*, 2013, vol. 85, pp. 6405–6413.

70. Mallat, Z., Hugel, B., Ohan, J., Leseche, G., Freyssinet, J.M., and Tedgui, A., *Circulation*, 1999, vol. 99, pp. 348–353.

71. Turiak, L., Misjak, P., Szabo, T.G., Aradi, B., Paloczi, K., Ozohanics, O., Drahos, L., Kittel, A., Falus, A., Buzas, E.I., and Vekey, K., *J. Proteomics*, 2011, vol. 74, pp. 2025–2033.

72. Lleo, A., Zhang, W., McDonald, W.H., Seeley, E.H., Leung, P.S.C., Coppel, R.L., Ansari, A.A., Adams, D.H., Afford, S., Invernizzi, P., and Gershwin, M.E., *Hepatology*, 2014, vol. 60, pp. 1314–1323.

73. Atkin-Smith, G.K., Tixeira, R., Paone, S., Mathivanan, S., Collins, C., Liem, M., Goodall, K.J., Ravichandran, K.S., Hulett, M.D., and Poon, I.K.H., *Nat. Commun.*, 2015, vol. 6, p. 7439.

74. Balkwill, F.R., Capasso, M., and Hagemann, T., *J. Cell Sci.*, 2012, vol. 125, pp. 5591–5596.

75. Koga, K., Matsumoto, K., Akiyoshi, T., Kubo, M., Yamanaka, N., Tasaki, A., Nakashima, H., Nakamura, M., Kuroki, S., Tanaka, M., and Katano, M., *Anticancer Res.*, 2005, vol. 25, pp. 3703–3707.

76. Demory, BecklerM., Higginbotham, J.N., Franklin, J.L., Ham, A.-J., Halvey, P.J., Imasuen, I.E., Whitwell, C., Li, M., Liebler, D.C., and Coffey, R.J., *Mol. Cell Proteomics*, 2013, vol. 12, pp. 343–355.

77. Soldevilla, B., Rodriguez, M., San, MillanC., Garcia, V., Fernandez-Perianez, R., Gil-Calderon, B., Martin, P., Garcia-Grande, A., Silva, J., Bonilla, F., and Dominguez, G., *Hum. Mol. Genet.*, 2014, vol. 23, pp. 467–478.

78. Qu, J.-L., Qu, X.-J., Zhao, M.-F., Teng, Y.-E., Zhang, Y., Hou, K.-Z., Jiang, Y.-H., Yang, X.-H., and Liu, Y.-P., *Dig. Liver Dis.*, 2009, vol. 41, pp. 875–880.

79. Kogure, T., Lin, W.-L., Yan, I.K., Braconi, C., and Patel, T., *Hepatology*, 2011, vol. 54, pp. 1237–1248.

80. Al-Nedawi, K., Meehan, B., Micallef, J., Lhotak, V., May, L., Guha, A., and Rak, J., *Nat. Cell Biol.*, 2008, vol. 10, pp. 619–624.

81. Meehan, K. and Vella, L.J., *Crit. Rev. Clin. Lab. Sci.,* 2016, vol. 53, pp. 121–131.

82. Hoshino, A., Costa-Silva, B., Shen, T.-L., Rodrigues, G., Hashimoto, A., Tesic, MarkM., Molina, H., Kohsaka, S., Di Giannatale, A., Ceder, S., Singh, S., Williams, C., Soplop, N., Uryu, K., Pharmer, L., King, T., Bojmar, L., Davies, A.E., Ararso, Y., Zhang, T., Zhang, H., Hernandez, J., Weiss, J.M., Dumont-Cole, V.D., Kramer, K., Wexler, L.H., Narendran, A., Schwartz, G.K., Healey, J.H., Sandstrom, P., Labori, K.J., Kure, E.H., Grandgenett, P.M., Hollingsworth, M.A., de Sousa, M., Kaur, S., Jain, M., Mallya, K., Batra, S.K., Jarnagin, W.R., Brady, M.S., Fodstad, O., Muller, V., Pantel, K., Minn, A.J., Bissell, M.J., Garcia, B.A., Kang, Y., Rajasekhar, V.K., Ghajar, C.M., Matei, I., Peinado, H., Bromberg, J., and Lyden, D., *Nature*, 2015, vol. 527, pp. 329–335.

83. Atay, S., Banskota, S., Crow, J., Sethi, G., Rink, L., and Godwin, A.K., *Proc. Natl. Acad. Sci. U. S. A.*, 2014, vol. 111, pp. 711–716.

84. Hood, J.L., San, R.S., and Wickline, S.A., *Cancer Res.*, 2011, vol. 71, pp. 3792–3801.

85. Costa-Silva, B., Aiello, N.M., Ocean, A.J., Singh, S., Zhang, H., Thakur, B.K., Becker, A., Hoshino, A., Mark, M.T., Molina, H., Xiang, J., Zhang, T., Theilen, T.-M., Garcia-Santos, G., Williams, C., Ararso, Y., Huang, Y., Rodrigues, G., Shen, T.-L., Labori, K.J., Lothe, I.M.B., Kure, E.H., Hernandez, J., Doussot, A., Ebbesen, S.H., Grandgenett, P.M., Hollingsworth, M.A., Jain, M., Mallya, K., Batra, S.K., Jarnagin, W.R., Schwartz, R.E., Matei, I., Peinado, H., Stanger, B.Z., Bromberg, J., and Lyden, D., *Nat. Cell Biol.*, 2015, vol. 17, pp. 816–826.

86. Ostenfeld, M.S., Jeppesen, D.K., Laurberg, J.R., Boysen, A.T., Bramsen, J.B., Primdal-Bengtson, B., Hendrix, A., Lamy, P., Dagnaes-Hansen, F., Rasmussen, M.H., Bui, K.H., Fristrup, N., Christensen, E.I., Nordentoft, I., Morth, J.P., Jensen, J.B., Pedersen, J.S., Beck, M., Theodorescu, D., Borre, M., Howard, K.A., Dyrskjot, L., and Orntoft, T.F., *Cancer Res.*, 2014, vol. 74, pp. 5758–5771.

87. Elmageed, Z.Y., Yang, Y., Thomas, R., Ranjan, M., Mondal, D., Moroz, K., Fang, Z., Rezk, B.M., Moparty, K., Sikka, S.C., Sartor, O., and Abdel-Mageed, A.B., *Stem. Cells*, 2014, vol. 32, pp. 983–997.

88. Ristorcelli, E., Beraud, E., Mathieu, S., Lombardo, D., and Verine, A., *Int. J. Cancer*, 2009, vol. 125, pp. 1016–1026.

89. Koga, K., Matsumoto, K., Akiyoshi, T., Kubo, M., Yamanaka, N., Tasaki, A., Nakashima, H., Nakamura, M., Kuroki, S., Tanaka, M., and Katano, M., *Anticancer Res.*, 2005, vol. 25, pp. 3703–3707.

90. Yang, L., Wu, X.-H., Wang, D., Luo, C.-L., and Chen, L.-X., *Mol. Med. Rep.*, 2013, vol. 8, pp. 1272–1278.

91. Cappellesso, R., Tinazzi, A., Giurici, T., Simonato, F., Guzzardo, V., Ventura, L., Crescenzi, M., Chiarelli, S., and Fassina, A., *Cancer Cytopathol.*, 2014, vol. 122, pp. 685–693.

92. Kahlert, C., Melo, S.A., Protopopov, A., Tang, J., Seth, S., Koch, M., Zhang, J., Weitz, J., Chin, L., Futreal, A., and Kalluri, R., *J. Biol. Chem.*, 2014, vol. 289, pp. 3869–3875.

93. Wang, J., Hendrix, A., Hernot, S., Lemaire, M., de Bruyne, E., van Valckenborgh, E., Lahoutte, T., de Wever, O., Vanderkerken, K., and Menu, E., *Blood*, 2014, vol. 124, pp. 555–566.

94. Federici, C., Petrucci, F., Caimi, S., Cesolini, A., Logozzi, M., Borghi, M., D'Ilio, S., Lugini, L., Violante, N., Azzarito, T., Majorani, C., Brambilla, D., and Fais, S., *PLoS One*, 2014, vol. 9, e88193.

95. Safaei, R., Larson, B.J., Cheng, T.C., Gibson, M.A., Otani, S., Naerdemann, W., and Howell, S.B., *Mol. Cancer Ther.*, 2005, vol. 4, pp. 1595–1604.

96. Shedden, K., Xie, X.T., Chandaroy, P., Chang, Y.T., and Rosania, G.R., *Cancer Res.*, 2003, vol. 63, pp. 4331–4337.

97. Ciravolo, V., Huber, V., Ghedini, G.C., Venturelli, E., Bianchi, F., Campiglio, M., Morelli, D., Villa, A., Della, MinaP., Menard, S., Filipazzi, P., Rivoltini, L., Tagliabue, E., and Pupa, S.M., *J. Cell Physiol.*, 2012, vol. 227, pp. 658–667.

98. Aung, T., Chapuy, B., Vogel, D., Wenzel, D., Oppermann, M., Lahmann, M., Weinhage, T., Menck, K., Hupfeld, T., Koch, R., Trumper, L., and Wulf, G.G., *Proc. Natl. Acad. Sci. U. S. A.*, 2011, vol. 108, pp. 15336–15341.

99. Xiao, X., Yu, S., Li, S., Wu, J., Ma, R., Cao, H., Zhu, Y., and Feng, J., *PLoS One*, 2014, vol. 9, e89534.

100. Corcoran, C., Rani, S., O'Brien, K., O'Neill, A., Prencipe, M., Sheikh, R., Webb, G., McDermott, R., Watson, W., Crown, J., and O'Driscoll, L., *PLoS One*, 2012, vol. 7, e50999.

101. Corcoran, C., Rani, S., and O'Driscoll, L., *Prostate*, 2014, vol. 74, pp. 1320–1334.

102. Challagundla, K.B., Wise, P.M., Neviani, P., Chava, H., Murtadha, M., Xu, T., Kennedy, R., Ivan, C., Zhang, X., Vannini, I., Fanini, F., Amadori, D., Calin, G.A., Hadjidaniel, M., Shimada, H., Jong, A., Seeger, R.C., Asgharzadeh, S., Goldkorn, A., and Fabbri, M., *J. Natl. Cancer Inst.*, 2015, vol. 107, djv135.

103. Takahashi, K., Yan, I.K., Kogure, T., Haga, H., and Patel, T., *FEBS Open Bio*, 2014, vol. 4, pp. 458–467.

104. Hu, Y., Yan, C., Mu, L., Huang, K., Li, X., Tao, D., Wu, Y., and Qin, J., *PLoS One*, 2015, vol. 10, e0125625.

105. King, H.W., Michael, M.Z., and Gleadle, J.M., *BMC Cancer*, 2012, vol. 12, p. 421.

106. Umezu, T., Tadokoro, H., Azuma, K., Yoshizawa, S., Ohyashiki, K., and Ohyashiki, J.H., *Blood*, 2014, vol. 124, pp. 3748–3757.

107. Svensson, K.J., Kucharzewska, P., Christianson, H.C., Skold, S., Lofstedt, T., Johansson, M.C., Morgelin, M., Bengzon, J., Ruf, W., and Belting, M., *Proc. Natl. Acad. Sci. U. S. A.*, 2011, vol. 108, pp. 13147–13152.

108. Kucharzewska, P., Christianson, H.C., Welch, J.E., Svensson, K.J., Fredlund, E., Ringnér, M., Mörgelin, M., Bourseau-Guilmain, E., Bengzon, J., and Belting, M., *Proc. Natl. Acad. Sci. U. S. A.*, 2013, vol. 110, pp. 7312–7317.

Translated by L. Onoprienko