



Review

Molecular Docking and Intracellular Translocation of Extracellular Vesicles for Efficient Drug Delivery

Yasunari Matsuzaka ^{1,2,*} and Ryu Yashiro ^{2,3}

¹ Division of Molecular and Medical Genetics, Center for Gene and Cell Therapy, The Institute of Medical Science, The University of Tokyo, Minato-ku 108-8639, Tokyo, Japan

² Administrative Section of Radiation Protection, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira 187-8551, Tokyo, Japan

³ Department of Infectious Diseases, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka-shi 181-8611, Tokyo, Japan

* Correspondence: yasunari80808@ims.u-tokyo.ac.jp; Tel.: +81-3-5449-5372

Abstract: Extracellular vesicles (EVs), including exosomes, mediate intercellular communication by delivering their contents, such as nucleic acids, proteins, and lipids, to distant target cells. EVs play a role in the progression of several diseases. In particular, programmed death-ligand 1 (PD-L1) levels in exosomes are associated with cancer progression. Furthermore, exosomes are being used for new drug-delivery systems by modifying their membrane peptides to promote their intracellular transduction via micropinocytosis. In this review, we aim to show that an efficient drug-delivery system and a useful therapeutic strategy can be established by controlling the molecular docking and intracellular translocation of exosomes. We summarise the mechanisms of molecular docking of exosomes, the biological effects of exosomes transmitted into target cells, and the current state of exosomes as drug delivery systems.

Keywords: cancer; exosomes; microRNAs; immune system; molecular docking; drug delivery



Citation: Matsuzaka, Y.; Yashiro, R. Molecular Docking and Intracellular Translocation of Extracellular Vesicles for Efficient Drug Delivery. *Int. J. Mol. Sci.* **2022**, *23*, 12971. <https://doi.org/10.3390/ijms232112971>

Academic Editors: María Yáñez-Mó, Francisco Sánchez-Madrid and Carlos Cabañas

Received: 10 August 2022

Accepted: 21 October 2022

Published: 26 October 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Intracellular communication mediated via extracellular vesicles (EVs) and drug-delivery systems based on EV biology have emerged as areas of investigation with a significant potential to impact human health [1–4]. EVs are comprised of lipid bilayer membranes and are classified into exosomes, microvesicles, and apoptotic bodies, mainly based on differences in their biogenesis [5–8]. Microvesicles emerge from the plasma membrane of the cell and have diameters of approximately 100 nm to 1000 nm [9,10]. Apoptotic bodies are giant vesicles formed from the plasma membrane during the induction of apoptosis and are approximately 1–5 µm in diameter [11–13]. Exosomes are formed within the intracellular multivesicular endosome (MVE) and are approximately 30–150 nm in diameter [14–30]. EVs are secreted by almost all cells. The release of the exosomes into the extracellular space is mediated by the fusion of the MVE membrane with the plasma membrane. Exosomes are found in various body fluids, such as plasma, serum, urine, saliva, and breast milk, and are also released in the culture supernatants of many cell lines [31–34]. They contain functional molecules, such as nucleic acids, microRNAs (miRNAs), messenger RNA (mRNA), and circulating RNA (circRNAs); metabolites and lipids on their membrane, such as phosphatidylserine; proteins, such as enzymes; and are characterized by some antigens, such as CD9, CD63, and CD81 [35–47]. These molecules are important for the characterisation of the cell type of origin for a given population of exosomes [48–95]. Secreted vesicles are transported by body fluids, such as blood, to cells where their impact is likely to be the greatest. The release of vesicles mediates intercellular communication [48–84]. In summary, exosomes reflect the characteristics of the cell from

which they were derived, are taken up by other cells, and are responsible for the intercellular transmission of information. In this review, we aim to summarise the intercellular mechanisms of exosomes, the biological effects of exosomes transmitted into target cells, and the current state of exosomes as drug-delivery systems. In addition, we summarize the latest studies on EVs as novel drug-delivery systems and their effects on cancer.

2. EVs in Cancer Metastasis and Malignant Transformation

EV-mediated intracellular communication plays a role not only in maintaining cell homeostasis, but also in disease progression [96–99]. Exosomes are associated with several diseases, including cancer metastasis, which is the invasion and spread of primary cancer cells into other organs [100–131]. Exosomes have been shown to play an important role in the formation of the cancer microenvironment and the mechanisms of cancer malignancy, such as cancer cell growth, infiltration, metastasis, and pre-metastasis niche [132–140]. Tumour-derived miRNA exosomes have been shown to affect tumour cells and stromal cells of the tumour microenvironment, such as fibroblasts and macrophages [141–145]. For example, miRNA exosomes secreted by cancer cells induce intratumoural angiogenesis, thereby promoting metastasis [145–149]. Moreover, miR-181c promotes the delocalization of actin fibres by downregulating the 3-phosphoinositide-dependent protein kinase 1 (PDPK1) gene [150].

Cancer-derived exosomes disrupt the blood–brain barrier and promote brain metastasis [151–154]. In breast cancer, tumour-derived exosomes containing miR-181c have been shown to promote cancer metastasis to the brain by disrupting the blood–brain barrier [150]. In addition, exosomes secreted by ovarian cancer containing matrix metalloproteinase 1 (MMP1) mRNAs induce peritoneal mesothelial cells to undergo apoptotic cell death, thereby promoting peritoneal cancer metastasis [155].

3. EV-Mediated Immune Escape of Cancer Cells

Tumours evade the immune systems by secreting exosomes containing proteins that suppress the immune response. A new pathway for such immune evasion has been identified in a laboratory model of skin cancer melanoma and patients suffering from the disease. Tumour cells release exosomes coated with programmed death-ligand 1 (PD-L1) proteins, which are immune checkpoint proteins that bind to immune cells to inactivate them [156–163]. This prevents immune cells from reaching tumour cells and attacking them. [164–178]. PD-L1 is present in exosomes released from melanoma cells [178–186]; however, exosomes derived from metastasised melanoma cells have a higher PD-L1 content than those derived from primary focal melanoma cells. Moreover, an electron microscope analysis revealed the PD-L1 protein was carried on the surface of the protein [187]. This suggests that PD-L1 on the surface of exosomes interacts directly with the immune cells. Furthermore, PDL1-positive exosomes mainly bind to cytotoxic T cells, preventing their proliferation and attack on cancer cells [159,188]. In a mouse model of melanoma that closely mimics human cancer, the injection of PDL-1-coated exosomes promoted tumour growth and reduced the number of T cells and other immune cells in and around the tumour (Figure 1) [162,173,189–192]. In addition, exosomes carrying PD-L1 have been identified in blood samples of patients with a history of breast cancer, melanoma, or lung cancer who had received treatments for their respective diseases [193–195].

Melanoma elicits a particularly strong immune response, and multiple immune checkpoint inhibitors have been approved by the US Food and Drug Administration for the treatment of melanoma [163–170]. Interestingly, based on PD-L1 levels in exosomes, patients who are most likely to respond to checkpoint inhibitors can be identified and the response to these drugs can be evaluated [162,194,196–199]. For example, compared to patients with high exosomal PD-L1 levels before treatment, those with lower levels responded remarkably better to treatments with the checkpoint inhibitor pembrolizumab (Keytruda), which can block PD-1, the immune cell binding partner of PD-L1 [185,196,198,200–205]. In contrast, after the start of treatment, higher exosomal PD-L1 levels reflected a reduction in

tumour size [206–208], indicating that two different mechanisms occur. Before treatment, exosomal PD-L1 levels likely reflect the size of the tumour and the extent of the disease. In other words, a high blood PD-L1 level indicates the presence of several tumours and is associated with a poor prognosis. After treatment, a rapid increase in exosomal PD-L1 in patients who responded to treatment indicates that T cells are activated and secrete more cytokines, such as interferon- γ (IFN- γ), which are signalling molecules that can stimulate the immune system [162,191,209–211]. In melanoma cell lines, treatment with IFN- γ has been shown to increase exosomal PD-L1 [162,212]. Moreover, analysis of patient samples revealed that exosomal PD-L1 levels tended to increase or decrease with increasing IFN- γ levels. Therefore, these findings also indicate that levels of exosomal PD-L1 in blood may help in selecting the appropriate treatment for different individuals. However, the exact mechanism by which exosomes carrying PD-L1 affect the immune response to tumours in patients with melanoma remains uncertain. Moreover, other types of immunomodulatory molecules may be present on the surface of these exosomes. Therefore, further research is needed using more samples from patients with melanoma and other cancer types and close comparison of PD-L1 in tumour biopsies with exosomes released from tumours should be observed. For example, approximately 40% of human melanoma cells express significant amounts of PD-L1 on their surfaces [213]. The presence of large amounts of exosomal PD-L1 in the blood of melanoma patients also suggests that PDL-1 has an overall effect on immunosuppression in those patients [161,162,182,186,214]. However, presently, there is no evidence that the immunity of patients with stage 4 melanoma is impaired.

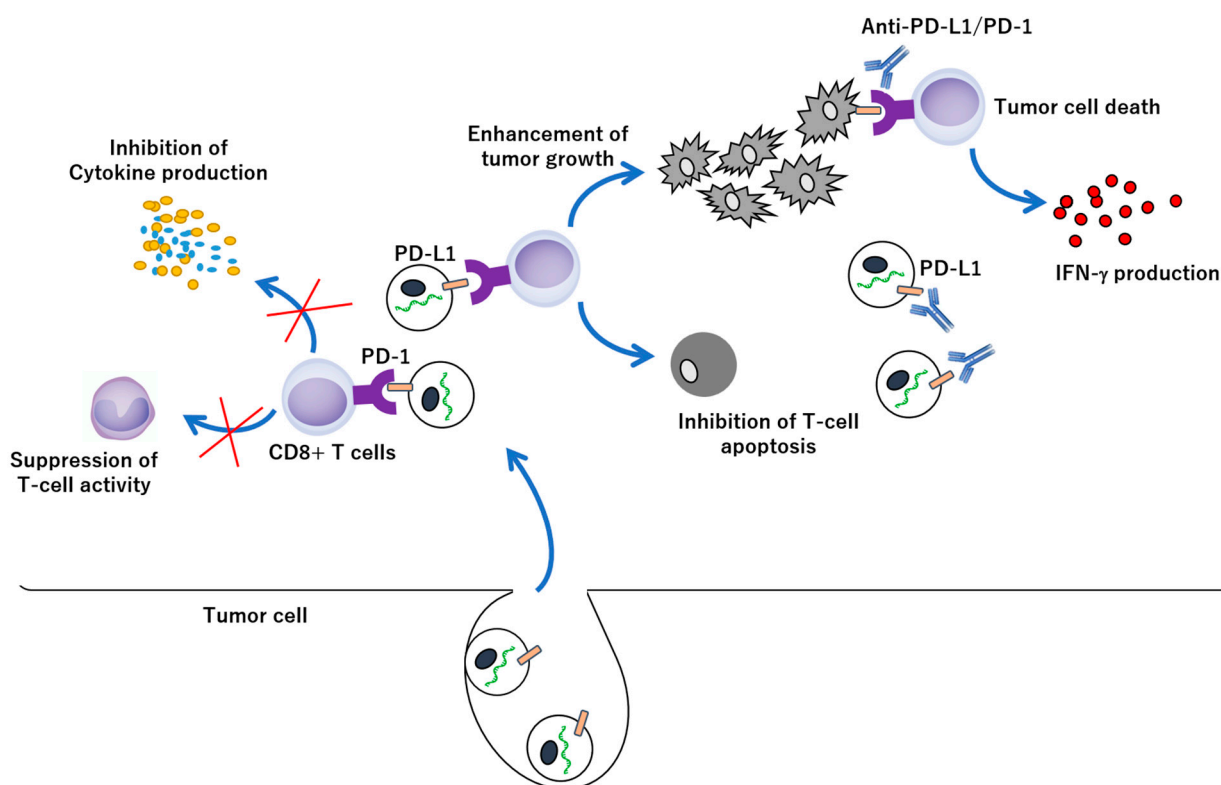


Figure 1. Exosomal PD-L1 in tumour growth and anti-PD-1/PD-L1 therapy. Exosomal PD-L1 secreted by tumour cells is leading to enhancement of tumour growth by reduction of T cell activity and inhibition of cytokine production, including IFN- γ and IL2, and limit effectiveness of anti-PD-1/PD-L1 therapy through binding to antibodies. On the other hand, elimination of the exosomal PD-L1 improves anti-PD-1/PD-L1 therapy.

For many years, exosomes have been thought to only function as molecular carriers that carry waste from cells; however, it has become clear that EVs affect various biological processes and diseases, including immune responses and cancer [215–232]. Nonetheless,

it is difficult to identify these exosomes. Moreover, the capacity of each exosome is only one-millionth of that of a typical cell, and most modern biomedical research tools are not suitable for the accurate and functional analysis of cargos within individual exosomes. Therefore, new tools and approaches would be useful to study these small vesicles in more detail.

4. Intracellular Translocation of Nucleic Acids and Proteins via EVs

EVs are highly expected to be next-generation drug carriers for the following reasons: (1) possible immunoregulation, (2) possible expression of membrane proteins by genetic engineering, (3) intracellular communication pathways, (4) low cytotoxicity, and (5) infinite secretion [1,233–241]. For example, small interfering RNA (siRNA) delivery for a BACE (β -site of Amyloid Precursor Protein cleaving enzyme) target using exosomes has proven to be beneficial in the treatment of Alzheimer's disease [242–244]. Furthermore, because exosomes that have miRNAs and enzyme-encapsulating cocktails, which have functions such as cell proliferation suppression and cell migration promotion, are naturally secreted from cells, they are highly expected to be used as drugs for treating several diseases [245–252]. The macropinocytosis pathway is important for the intracellular translocation of exosomes [253–258]. Therefore, by modifying the membrane surface of exosomes with a functional peptide to induce macropinocytosis, it is possible to considerably increase the efficiency of the intracellular delivery of exosomes [254,255,257].

5. EV Uptake in Target Cells via Macropinocytosis

Eukaryotic cells take up molecules, such as extracellular proteins and lipoproteins, by a process called endocytosis, which includes clathrin-dependent or -independent endocytosis and micropinocytosis (Figure 2) [259–269]. In clathrin-dependent endocytosis, when a ligand molecule binds to a receptor on the plasma membrane, a clathrin molecule binds to the cytosol via an AP2 adaptor protein, and a ball-shaped structure of the plasma membrane is formed [270–273].

In addition, dynamin then separates the endosome from the plasma membrane via clathrin-dependent endocytosis [274–276]. These formed endosomes usually measure up to approximately 120 nm in diameter because clathrin limits the size of endosomes [277–279]. Therefore, in normal clathrin-dependent endocytosis, the intracellular translocation of EVs is inefficient. By contrast, macropinocytosis can take up extracellular molecules with a diameter greater than 1 μ m, including nutrients, into cells. Macropinocytosis is a clathrin-independent pathway, characterised by actin-dependent reorganisations (lamellipodia) of the plasma membrane to form macropinosomes [280]. Macropinocytosis is induced by the activation of various receptors, such as the epidermal growth factor receptor (EGFR), which is highly expressed in tumour cells, such as human epidermal cancer A431 and the chemokine receptor CXCR4 [253,281–297].

Furthermore, *in vitro* experiments have revealed that human pancreatic cancer-derived MIA PaCa cells, which highly induce macropinocytosis, have high exosomal migration efficiency [253,298,299]. Normally, the exosome membrane is negatively charged (zeta potential is approximately -10 mV); therefore, it repels with the negatively charged plasma membrane [300–303]. However, in the macropinocytosis pathway, exosomes that do not easily interact with the plasma membrane can be effectively wrapped and incorporated into cells using ruffling [296,304]. These findings highly suggest that macropinocytosis contributes to intercellular communication.

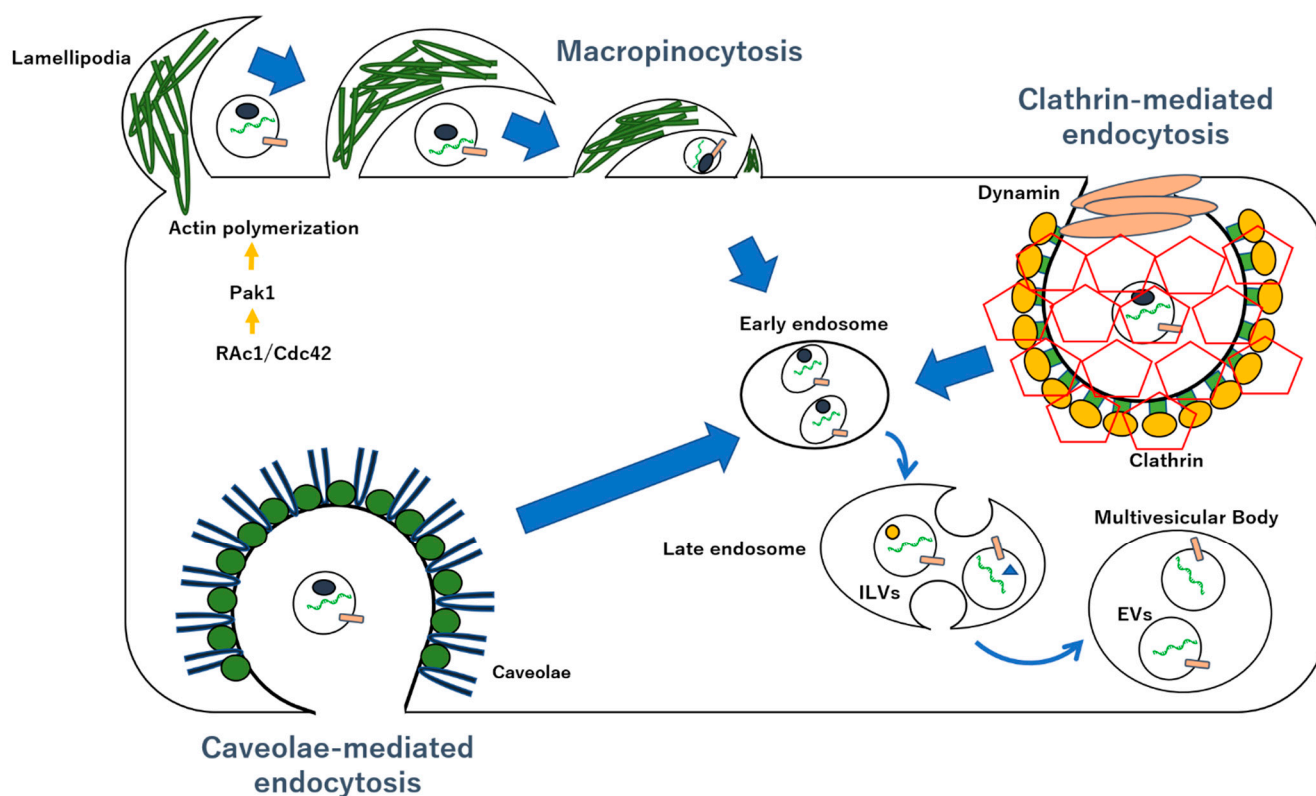


Figure 2. Uptake mechanisms for the transport of EVs. Macropinocytosis is characterized by signal transduction involving the activation of the small G-protein Rac, which leads to polymerization of the actin backbone and formation of lamellipodia in the plasma membrane. Utilizing the lamellipodia structure of the plasma membrane, cells usually surround the extracellular fluid with a size of more than 1 μm , eventually forming vacuoles and taking them into the cell. Clathrin-mediated endocytosis involves five steps, including depression formation of membrane, accumulation of cargo, membrane encapsulation (formation of clathrin-coated pits), cutting, and uncoating, to deliver membrane vesicles containing cargo into the cell. The formation of caveolar endocytic vesicles requires the oligomerization of caveolin, which leads to the formation of caveolin-rich microdomains in the plasma membrane. ILVs: intraluminal vesicles.

In pancreatic cancer, exosomes derived from normal fibroblast-like mesenchymal cells were engineered to carry siRNA or shRNA specific to oncogenic KRAS, which is a common mutation in pancreatic cancer. These exosomes were effectively taken up by target cells by macropinocytosis and exerted a remarkable effect in suppressing pancreatic cancer cell growth *in vivo* [281,305–308]. Moreover, in lung cancer, gefitinib (Iressa), an anticancer drug that inhibits the epidermal growth factor receptor (EGFR), was shown to increase the intracellular translocation of exosomes, but decrease that of liposomes, which are typically used for drug-delivery systems [309]. In addition, compared to liposome-encapsulated doxorubicin, exosome-encapsulated doxorubicin results in robustly higher anticancer activity against non-small cell lung cancer [310,311]. Furthermore, degradation of the exosomal membrane proteins further enhanced intracellular migration induced by gefitinib treatment [304]; thus, exosomal membrane lipids may contribute to the promotion of intracellular translocation during gefitinib treatment. Additionally, a macropinocytosis inhibitor was shown to remarkably suppress the growth of pancreatic cancer cells both *in vitro* and *in vivo* [288–292]. Thus, macropinocytosis pathway inhibitors can be used to suppress the progression of pancreatic cancer. These findings suggest that drug applications from a new perspective are highly beneficial to treat cancer.

6. Techniques for Functional Peptide Modifications on the Exosomal Membrane

A previous study on the intracellular uptake of exosomes using a functional peptide modification technique on the exosomal membrane has revealed its importance for the intracellular translocation of exosomes [258,298,312]. Two simple techniques for binding peptides to the exosomal membrane without modifying the components of the membrane have been reported: (1) acylating a peptide such as a stearyl group and (2) using a peptide with a linker including a succinimide group [298,313]. In the method of acylating a peptide with a stearyl group, when the peptide is synthesised on beads by the Fmoc solid phase method, the N-terminal is dehydrated and condensed with stearic acid, and then deprotected and purified to obtain the acylated target peptide [254,258,314]. For example, a peptide with a stearyl group can easily be inserted into an exosomal membrane with an acylated hydrophobic part, and the peptide can be presented on the exosomal membrane simply by mixing the peptide with the exosome in a solution [258,315]. Peptides that are not present in the exosome membrane can be removed by ultrafiltration. This method does not require consideration of the sequence of the peptide; however, for highly hydrophobic peptides, the solubility may deteriorate owing to the addition of a hydrophobic group to the peptide. In such cases, the balance between the control of the hydrophobic group to be acylated and the degree of insertion into the exosome membrane should be considered. Furthermore, in the method using a peptide with a linker including a succinimide group, it is possible to covalently bind the target peptide and the exosomal membrane protein using a divalent linker, such as N-(6-maleimidocaproyloxy) sulphosuccinimide and sodium salt (sulpho-EMCS) [257]. During peptide synthesis, after introducing cysteine residues into the peptide sequence, an acetylation cap with acetic anhydride is applied at the N-terminal cysteine residue side chain of the purified target, and the maleimide group of EMCS is bound by Michael addition and purified again. Next, by mixing the purified peptide and exosome, the succinimide group possessed by the linker of the peptide reacts with the membrane protein amino group of the exosome, and the target peptide and exosome are covalently attached. This method can be used when an amino group, such as lysine or a cysteine residue, does not exist in the peptide sequence to be originally bound. However, it may be necessary to introduce an unnatural amino acid into the amino acid sequence and use a linker bond using click chemistry. When the first method is used, the membrane protein of the exosome is hardly affected and the peptide can be modified, whereas in the second method, since a covalent bond is formed on the side chain of the constituent amino acids of the membrane protein, the original function of the membrane protein may be affected. However, because the second method modifies the peptide by covalent bonding, peptide retention on the exosomal membrane is higher than that of the anchor type inserted into the membrane using the first method. Therefore, it is evident that the macropinocytosis pathway is important for the intracellular translocation of exosomes [253]. The development of a technique that can induce macropinocytosis using exosomes can enhance intracellular migration.

A membrane-permeable arginine peptide-modified exosome that induces macropinocytosis has been developed. In addition, the human immunodeficiency virus (HIV)-1 encodes the transcription factor trans-activator of transcription (Tat) protein-derived peptides and oligoarginines, which are cell-penetrating peptides that can easily penetrate cells (CPPs) [316]. CPPs contain many arginine residues in their sequence; therefore, they accumulate in the plasma membrane because of their interactions with heparan sulphate of the sugar chain of proteoglycan in the membrane. As a result, clustering of proteoglycan (syndecan-4), intracellular binding of protein kinase C, alpha (PKC α) to proteoglycan, and signal transduction occur. Moreover, EVs can be efficiently taken up into cells by the activation of the small G protein Rac1, which induces macropinocytosis due to the remodelling of the actin skeleton [316]. Therefore, exosomes induce macropinocytosis in target cells by binding to membrane-permeable arginine peptides. Moreover, the EV uptake efficiency depends on the number of peptides bound to the exosome membrane. When octaarginine (stearyl-R8), which is a typical membrane-permeable arginine peptide with the previously

mentioned stearyl group at the N-terminus, is mixed with CD63-GFP (green fluorescent protein)-exosomes to modify the peptide on the exosome, exosomes can act as scaffolds to promote the clustering of syndecan-4 on the plasma membrane of target cells and induce macropinocytosis with foliate pseudopodia by modifying stearyl-R8. This can remarkably increase the efficiency of the intracellular translocation of exosomes. Notably, this method caused almost no cytotoxicity [258].

In addition, the clustering of proteoglycans by the peptide and the induction of macropinocytosis are affected by the number of arginine residues in the sequence [316,317]. Furthermore, the binding of oligoarginines with different numbers of arginine residues to the membrane surface of CD63-GFP-exosome does not affect the morphology of the exosomes. Notably, this method did not exhibit cytotoxic effects. In addition, as previously mentioned, despite the negative charge of the exosomal membrane, when oligoarginine and exosomes were simply mixed without using a divalent linker, no increase in the efficiency of intracellular translocation of exosomes was observed with any oligoarginine [257]. Thus, the strong binding of a functional peptide to the exosomal membrane using the method previously discussed is important for fully exploiting the functionality of the peptide. It was also reported that the activity of drug-encapsulated exosomes was markedly higher in exosomes bound with the R16 peptide, which has a relatively low intracellular translocation compared with those bound to R8 and R12 peptides, which have a higher translocation. This suggests that the cytosolic release efficiency of modified exosomes after intracellular translocation is high, although R16 peptides have lower intracellular translocation than the R8 and R12 peptides [257]. Therefore, when selecting a functional peptide, a well-balanced peptide must be selected by considering not only the intracellular transfer efficiency, but also the release efficiency after intracellular transfer.

Normally, when the drug is delivered intracellularly by endocytosis or macropinocytosis, the contents of the endosome are degraded by various enzymes [318,319]. Therefore, the drug must escape into the cytosol before lysosomal degradation. Nakase et al. have developed an efficient cytosolic delivery technique for proteins using the GALA peptide, which is a pH-sensitive membrane fusion peptide [320,321]. The GALA peptide (amino acid sequence: WEAALAEALAEALAEHLAEALAEALEALAA) is an artificial peptide that mimics the membrane fusion protein of a virus composed of 30-residue amino acids. When the pH is neutral, the peptide has almost no secondary structure; however, as the pH decreases, the helix content increases, facilitating the incorporation of the peptide into the membrane, which promotes membrane destabilisation and fusion [320,321]. This GALA peptide is rich in glutamate residues and negatively charged. However, since the cell plasma membrane is also negatively charged, the intracellular transferability of the GALA peptide alone is extremely low. Therefore, the formation of a complex between a cationic lipid and GALA significantly increased the intracellular translocation of the GALA peptide. Furthermore, by binding molecules, such as proteins to be carried to the cytosol, to the GALA peptide and forming a complex with the cationic lipid, this complex is taken up into cells by endocytosis, and the target molecule bound to the GALA peptide can be effectively released into the cytosol [321,322]. Although the use of a large number of cationic lipids causes cytotoxicity, cells hardly uptake GALA even if they uptake exosomes; therefore, complex formation using lipids is important. Furthermore, when ammonium chloride was used to suppress the decrease in pH in endosomes, the cytosolic escape effect of the GALA peptide was markedly reduced. This finding indicates that endosome maturation is important for peptide function. In addition, it is important to optimise the concentration in complex formation because the difference in the concentration of the GALA peptide affects complex formation and cytosol escape efficiency. This epoch-making method can easily promote the cytosolic release of exosome-encapsulated molecules by simply mixing them with exosomes. Therefore, it can be applied to various drug-encapsulating exosomes (including miRNAs) in the future, such as miRNA-encapsulating exosomes in myocytes [323].

7. Storages of EVs as a Long-Term Strategy

It is important to establish a preservation method for drug-encapsulating exosomes. Exosomes can be stored in a refrigerator for approximately 1–2 weeks at the most but can be frozen for several months. However, repeated freezing and thawing are known to have a serious effect on the morphology of exosomes. For preservation methods, such as freeze-drying exosomes bound to R16 peptide and then adding water to restore them, the R16 peptide-modified exosomes were shown to be hardly affected [260]. In contrast, for R16-bound exosomes containing drugs, as described above, freeze-drying resulted in a considerable reduction in drug activity. Therefore, the efficiency of the cytosolic release of the encapsulated drug after intracellular transfer may be reduced after lyophilisation. The storage capacity of EVs can depend on their number, size, function, temperature, duration, and freeze–thaw cycles [324–329].

8. Clinical Application

EVs are attracting attention as drug carriers that deliver nucleic acid medicine, which is a general term for medicines that do not directly encode proteins, but directly act on DNA, RNA, or chemically synthesized oligonucleotides on proteins, to the affected area [330–335]. Types of nucleic acid drugs include antisense nucleic acids, siRNA, miRNA, decoy nucleic acids, nucleic acid aptamers, etc. These are attracting attention as new therapeutic agents following low molecular weight drugs and antibody drugs that have already been clinically applied. On the other hand, nucleic acid drugs are easily degraded in blood, which contains many digestive enzymes. Therefore, in order to obtain clinical efficacy against various diseases through blood, a drug carrier that is safe to the body, prevents degradation by digestive enzymes, and selectively delivers nucleic acid medicines to the affected area is required. EVs are stable in blood due to a lipid bilayer membrane. They are about 100 nm in size, and renal excretion, immune mechanism, and enhanced permeation and retention effect are optimal. EVs are secreted by various cells in the body, and compared to artificially constructed drug carriers, immune reactions are less likely to occur. Clinical trials of EVs have already been conducted and their safety has been investigated. It is suggested that EVs are transported in an organ-specific manner. In fact, many researchers have already begun to report on *in vivo* studies in which nucleic acid drugs, such as siRNA, are encapsulated in EVs [336–340]. Furthermore, treatment methods targeting EVs are being investigated, and some are already undergoing clinical trials. The main therapeutic strategies are roughly divided into two: one is a method of targeting and removing/inhibiting harmful EVs themselves, and the other is a method of utilizing beneficial EVs. The former is thought to inhibit EVs secretion, remove EVs present in the blood, and inhibit EVs uptake. Further, Nishida-Aoki et al. reported that the EVs removal by tail vein administration of antibodies to xenograft mouse models using human cancer cell lines can suppress cancer metastasis [341]. These results suggest that EVs-targeted therapy may have clinical efficacy. The latter mainly includes the use of EVs loaded with antigenic peptides as vaccines and the use of mesenchymal stem cell (MSC)-derived EVs. In particular, MSC-derived EVs have already been clinically tested for steroid-refractory graft-versus-host disease, and there have been reports of significant improvement in symptoms without obvious adverse effects [342–344].

9. Conclusions

The intracellular transduction of exosomes, including miRNAs and proteins, is regulated by clathrin-dependent or -independent endocytosis and micropinocytosis. By controlling the organ or tissue tropism of exosomes and promoting their intracellular translocation, we expect to construct safe and effective drug delivery systems. Moreover, modification of the peptides on the surface of the exosomes is a novel technique to generate drug-encapsulating exosomes. Furthermore, modified exosomes whose surfaces are modified with binding ligands can be expected to be highly safe and result in effective transduction of DDS by controlling tissue tropism *in vivo*. Thus, it is expected to become a touchstone

for the establishment of new treatment strategies for various diseases, including cancer, especially for intractable diseases for which no treatment methods have been available thus far.

Author Contributions: Writing, review, and editing, Y.M.; supervision, R.Y.; funding acquisition, Y.M. All authors have read and agreed to the published version of the manuscript.

Funding: This review was funded by the Fukuda Foundation for Medical Technology, and APC was funded by the Fukuda Foundation for Medical Technology.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Matsuzaka, Y.; Yashiro, R. Extracellular Vesicles as Novel Drug-Delivery Systems through Intracellular Communications. *Membranes* **2022**, *12*, 550. [[CrossRef](#)] [[PubMed](#)]
2. Giovannelli, P.; Di Donato, M.; Galasso, G.; Monaco, A.; Licitra, F.; Perillo, B.; Migliaccio, A.; Castoria, G. Communication between cells: Exosomes as a delivery system in prostate cancer. *Cell Commun. Signal.* **2021**, *19*, 110. [[CrossRef](#)]
3. Choi, H.; Choi, Y.; Yim, H.Y.; Mirzaaghasi, A.; Yoo, J.K.; Choi, C. Biodistribution of Exosomes and Engineering Strategies for Targeted Delivery of Therapeutic Exosomes. *Tissue Eng. Regen. Med.* **2021**, *18*, 499–511. [[CrossRef](#)]
4. Gaurav, I.; Thakur, A.; Iyaswamy, A.; Wang, X.; Chen, X.; Yang, Z. Factors Affecting Extracellular Vesicles Based Drug Delivery Systems. *Molecules* **2021**, *26*, 1544. [[CrossRef](#)] [[PubMed](#)]
5. Qin, X.; Zhou, Y.; Jia, C.; Chao, Z.; Qin, H.; Liang, J.; Liu, X.; Liu, Z.; Sun, T.; Yuan, Y.; et al. Caspase-1-mediated extracellular vesicles derived from pyroptotic alveolar macrophages promote inflammation in acute lung injury. *Int. J. Biol. Sci.* **2022**, *18*, 1521–1538. [[CrossRef](#)] [[PubMed](#)]
6. Tayebi, M.; Yang, D.; Collins, D.J.; Ai, Y. Deterministic Sorting of Submicrometer Particles and Extracellular Vesicles Using a Combined Electric and Acoustic Field. *Nano Lett.* **2021**, *21*, 6835–6842. [[CrossRef](#)] [[PubMed](#)]
7. Nishimura, T.; Oyama, T.; Hu, H.T.; Fujioka, T.; Hanawa-Suetsugu, K.; Ikeda, K.; Yamada, S.; Kawana, H.; Saigusa, D.; Ikeda, H.K.; et al. Filopodium-derived vesicles produced by MIM enhance the migration of recipient cells. *Dev. Cell* **2021**, *56*, 842–859.e8. [[CrossRef](#)]
8. Liu, T.; Hooda, J.; Atkinson, J.M.; Whiteside, T.L.; Oesterreich, S.; Lee, A.V. Exosomes in Breast Cancer—Mechanisms of Action and Clinical Potential. *Mol. Cancer Res.* **2021**, *19*, 935–945. [[CrossRef](#)] [[PubMed](#)]
9. Lazar, S.; Goldfinger, L.E. Platelets and extracellular vesicles and their cross talk with cancer. *Blood* **2021**, *137*, 3192–3200. [[CrossRef](#)]
10. Menck, K.; Sivaloganathan, S.; Bleckmann, A.; Binder, C. Microvesicles in Cancer: Small Size, Large Potential. *Int. J. Mol. Sci.* **2020**, *21*, 5373. [[CrossRef](#)]
11. Wang, C.; Liu, J.; Yan, Y.; Tan, Y. Role of Exosomes in Chronic Liver Disease Development and Their Potential Clinical Applications. *J. Immunol. Res.* **2022**, *2022*, 1695802. [[CrossRef](#)] [[PubMed](#)]
12. Shang, X.; Fang, Y.; Xin, W.; You, H. The Application of Extracellular Vesicles Mediated miRNAs in Osteoarthritis: Current Knowledge and Perspective. *J. Inflamm. Res.* **2022**, *15*, 2583–2599. [[CrossRef](#)]
13. Fu, Y.; Sui, B.; Xiang, L.; Yan, X.; Wu, D.; Shi, S.; Hu, X. Emerging understanding of apoptosis in mediating mesenchymal stem cell therapy. *Cell Death Dis.* **2021**, *12*, 596. [[CrossRef](#)] [[PubMed](#)]
14. Xiong, Y.; Song, J.; Huang, X.; Pan, Z.; Goldbrunner, R.; Stavrinou, L.; Lin, S.; Hu, W.; Zheng, F.; Stavrinou, P. Exosomes Derived from Mesenchymal Stem Cells: Novel Effects in the Treatment of Ischemic Stroke. *Front. Neurosci.* **2022**, *16*, 899887. [[CrossRef](#)]
15. Xu, Y.; Hu, Y.; Xu, S.; Liu, F.; Gao, Y. Exosomal microRNAs as Potential Biomarkers and Therapeutic Agents for Acute Ischemic Stroke: New Expectations. *Front. Neurol.* **2022**, *12*, 747380. [[CrossRef](#)] [[PubMed](#)]
16. Bischoff, J.P.; Schulz, A.; Morrison, H. The role of exosomes in intercellular and inter-organ communication of the peripheral nervous system. *FEBS Lett.* **2022**, *596*, 655–664. [[CrossRef](#)]
17. Chen, Y.; Zhao, Y.; Yin, Y.; Jia, X.; Mao, L. Mechanism of cargo sorting into small extracellular vesicles. *Bioengineered* **2021**, *12*, 8186–8201. [[CrossRef](#)] [[PubMed](#)]
18. Waldenmaier, M.; Seibold, T.; Seufferlein, T.; Eiseler, T. Pancreatic Cancer Small Extracellular Vesicles (Exosomes): A Tale of Short- and Long-Distance Communication. *Cancers* **2021**, *13*, 4844. [[CrossRef](#)] [[PubMed](#)]
19. Kaur, S.; Verma, H.; Dhiman, M.; Tell, G.; Gigli, G.L.; Janes, F.; Mantha, A.K. Brain Exosomes: Friend or Foe in Alzheimer's Disease? *Mol. Neurobiol.* **2021**, *58*, 6610–6624. [[CrossRef](#)] [[PubMed](#)]
20. Liu, J.; Ren, L.; Li, S.; Li, W.; Zheng, X.; Yang, Y.; Fu, W.; Yi, J.; Wang, J.; Du, G. The biology, function, and applications of exosomes in cancer. *Acta Pharm. Sin. B* **2021**, *11*, 2783–2797. [[CrossRef](#)]

21. Yang, Y.; Yuan, L.; Du, X.; Zhou, K.; Qin, L.; Wang, L.; Yang, M.; Wu, M.; Zheng, Z.; Xiang, Y.; et al. Involvement of epithelia-derived exosomes in chronic respiratory diseases. *Biomed. Pharmacother* **2021**, *143*, 112189. [[CrossRef](#)]
22. U Stotz, H.; Brotherton, D.; Inal, J. Communication is key: Extracellular vesicles as mediators of infection and defence during host-microbe interactions in animals and plants. *FEMS Microbiol. Rev.* **2022**, *46*, fuab044. [[CrossRef](#)]
23. Hade, M.D.; Suire, C.N.; Suo, Z. Mesenchymal Stem Cell-Derived Exosomes: Applications in Regenerative Medicine. *Cells* **2021**, *10*, 1959. [[CrossRef](#)] [[PubMed](#)]
24. Thej, C.; Kishore, R. Unfathomed Nanomessages to the Heart: Translational Implications of Stem Cell-Derived, Progenitor Cell Exosomes in Cardiac Repair and Regeneration. *Cells* **2021**, *10*, 1811. [[CrossRef](#)]
25. Whiteside, T.L.; Diergaarde, B.; Hong, C.S. Tumor-Derived Exosomes (TEX) and Their Role in Immuno-Oncology. *Int. J. Mol. Sci.* **2021**, *22*, 6234. [[CrossRef](#)] [[PubMed](#)]
26. Gurunathan, S.; Kang, M.H.; Kim, J.H. A Comprehensive Review on Factors Influences Biogenesis, Functions, Therapeutic and Clinical Implications of Exosomes. *Int. J. Nanomed.* **2021**, *16*, 1281–1312. [[CrossRef](#)]
27. Rezaie, J.; Aslan, C.; Ahmadi, M.; Zolbanin, N.M.; Kashanchi, F.; Jafari, R. The versatile role of exosomes in human retroviral infections: From immunopathogenesis to clinical application. *Cell Biosci.* **2021**, *11*, 19. [[CrossRef](#)] [[PubMed](#)]
28. Koohsarian, P.; Talebi, A.; Rahnama, M.A.; Zomorrod, M.S.; Kaviani, S.; Jalili, A. Reviewing the role of cardiac exosomes in myocardial repair at a glance. *Cell Biol. Int.* **2021**, *45*, 1352–1363. [[CrossRef](#)] [[PubMed](#)]
29. Murugesan, S.; Saravanakumar, L.; Powell, M.F.; Rajasekaran, N.S.; Kannappan, R.; Berkowitz, D.E. Role of exosomal microRNA signatures: An emerging factor in preeclampsia-mediated cardiovascular disease. *Placenta* **2021**, *103*, 226–231. [[CrossRef](#)] [[PubMed](#)]
30. Kita, S.; Shimomura, I. Stimulation of exosome biogenesis by adiponectin, a circulating factor secreted from adipocytes. *J. Biochem.* **2021**, *169*, 173–179. [[CrossRef](#)] [[PubMed](#)]
31. Jayaseelan, V.P. Emerging role of exosomes as promising diagnostic tool for cancer. *Cancer Gene Ther.* **2020**, *27*, 395–398. [[CrossRef](#)] [[PubMed](#)]
32. Hesari, A.; Golrokh Moghadam, S.A.; Siasi, A.; Rahmani, M.; Behboodi, N.; Rastgar-Moghadam, A.; Ferns, G.A.; Ghasemi, F.; Avan, A. Tumor-derived exosomes: Potential biomarker or therapeutic target in breast cancer? *J. Cell Biochem.* **2018**, *119*, 4236–4240. [[CrossRef](#)] [[PubMed](#)]
33. Li, S.R.; Man, Q.W.; Gao, X.; Lin, H.; Wang, J.; Su, F.C.; Wang, H.Q.; Bu, L.L.; Liu, B.; Chen, G. Tissue-derived extracellular vesicles in cancers and non-cancer diseases: Present and future. *J. Extracell. Vesicles* **2021**, *10*, e12175. [[CrossRef](#)] [[PubMed](#)]
34. Jin, C.; Wu, P.; Li, L.; Xu, W.; Qian, H. Exosomes: Emerging Therapy Delivery Tools and Biomarkers for Kidney Diseases. *Stem Cells Int.* **2021**, *2021*, 7844455. [[CrossRef](#)] [[PubMed](#)]
35. Wang, J.; Wang, J.; Li, X.; Shu, K. Cell-Derived Exosomes as Therapeutic Strategies and Exosome-Derived microRNAs as Biomarkers for Traumatic Brain Injury. *J. Clin. Med.* **2022**, *11*, 3223. [[CrossRef](#)] [[PubMed](#)]
36. Mousavi, S.M.; Amin Mahdian, S.M.; Ebrahimi, M.S.; Taghizadieh, M.; Vosough, M.; Sadri Nahand, J.; Hosseindoost, S.; Vousooghi, N.; Javar, H.A.; Larijani, B.; et al. Microfluidics for detection of exosomes and microRNAs in cancer: State of the art. *Mol. Ther. Nucleic Acids* **2022**, *28*, 758–791. [[CrossRef](#)]
37. Sun, H.; Sun, R.; Song, X.; Gu, W.; Shao, Y. Mechanism and clinical value of exosomes and exosomal contents in regulating solid tumor radiosensitivity. *J. Transl. Med.* **2022**, *20*, 189. [[CrossRef](#)]
38. Suire, C.N.; Hade, M.D. Extracellular Vesicles in Type 1 Diabetes: A Versatile Tool. *Bioengineering* **2022**, *9*, 105. [[CrossRef](#)]
39. Nikdoust, F.; Pazoki, M.; Mohammadtaghizadeh, M.; Aghaali, M.K.; Amrovani, M. Exosomes: Potential Player in Endothelial Dysfunction in Cardiovascular Disease. *Cardiovasc. Toxicol.* **2022**, *22*, 225–235. [[CrossRef](#)]
40. Feng, Z.Y.; Zhang, Q.Y.; Tan, J.; Xie, H.Q. Techniques for increasing the yield of stem cell-derived exosomes: What factors may be involved? *Sci. China Life Sci.* **2022**, *65*, 1325–1341. [[CrossRef](#)] [[PubMed](#)]
41. Rajool Dezfuly, A.; Safaee, A.; Salehi, H. Therapeutic effects of mesenchymal stem cells-derived extracellular vesicles' miRNAs on retinal regeneration: A review. *Stem Cell Res. Ther.* **2021**, *12*, 530. [[CrossRef](#)] [[PubMed](#)]
42. Aoi, W.; Tanimura, Y. Roles of Skeletal Muscle-Derived Exosomes in Organ Metabolic and Immunological Communication. *Front. Endocrinol* **2021**, *12*, 697204. [[CrossRef](#)] [[PubMed](#)]
43. Alharbi, M.G.; Lee, S.H.; Abdelazim, A.M.; Saadeldin, I.M.; Abomughaid, M.M. Role of Extracellular Vesicles in Compromising Cellular Resilience to Environmental Stressors. *Biomed. Res. Int.* **2021**, *2021*, 9912281. [[CrossRef](#)] [[PubMed](#)]
44. Mirzaei, R.; Zamani, F.; Hajibaba, M.; Rasouli-Saravani, A.; Noroozbeygi, M.; Gorgani, M.; Hosseini-Fard, S.R.; Jalalifar, S.; Ajdarkosh, H.; Abedi, S.H.; et al. The pathogenic, therapeutic and diagnostic role of exosomal microRNA in the autoimmune diseases. *J. Neuroimmunol.* **2021**, *358*, 577640. [[CrossRef](#)]
45. Bahrami, A.; Binabajm, M.M.; Ferns, A.G. Exosomes: Emerging modulators of signal transduction in colorectal cancer from molecular understanding to clinical application. *Biomed. Pharmacother.* **2021**, *141*, 111882. [[CrossRef](#)] [[PubMed](#)]
46. Liew, F.F.; Chew, B.C.; Ooi, J. Wound Healing Properties of Exosomes—A Review and Modelling of Combinatorial Analysis Strategies. *Curr. Mol. Med.* **2022**, *22*, 165–191. [[CrossRef](#)] [[PubMed](#)]
47. Yamada, M. Extracellular vesicles: Their emerging roles in the pathogenesis of respiratory diseases. *Respir. Investig.* **2021**, *59*, 302–311. [[CrossRef](#)] [[PubMed](#)]

48. Huang, Y.; Kanada, M.; Ye, J.; Deng, Y.; He, Q.; Lei, Z.; Chen, Y.; Li, Y.; Qin, P.; Zhang, J.; et al. Exosome-mediated remodeling of the tumor microenvironment: From local to distant intercellular communication. *Cancer Lett.* **2022**, *543*, 215796. [[CrossRef](#)] [[PubMed](#)]
49. Han, Z.; Chen, H.; Guo, Z.; Shen, J.; Luo, W.; Xie, F.; Wan, Y.; Wang, S.; Li, J.; He, J. Circular RNAs and Their Role in Exosomes. *Front. Oncol.* **2022**, *12*, 848341. [[CrossRef](#)]
50. Thakur, A.; Johnson, A.; Jacobs, E.; Zhang, K.; Chen, J.; Wei, Z.; Lian, Q.; Chen, H.J. Energy Sources for Exosome Communication in a Cancer Microenvironment. *Cancers* **2022**, *14*, 1698. [[CrossRef](#)] [[PubMed](#)]
51. Hsu, M.T.; Wang, Y.K.; Tseng, Y.J. Exosomal Proteins and Lipids as Potential Biomarkers for Lung Cancer Diagnosis, Prognosis, and Treatment. *Cancers* **2022**, *14*, 732. [[CrossRef](#)] [[PubMed](#)]
52. Mahmoudi, A.; Butler, A.E.; Jamialahmadi, T.; Sahebkar, A. The role of exosomal miRNA in nonalcoholic fatty liver disease. *J. Cell Physiol.* **2022**, *237*, 2078–2094. [[CrossRef](#)] [[PubMed](#)]
53. Yun, B.D.; Choi, Y.J.; Son, S.W.; Cipolla, G.A.; Berti, F.C.B.; Malheiros, D.; Oh, T.J.; Kuh, H.J.; Choi, S.Y.; Park, J.K. Oncogenic Role of Exosomal Circular and Long Noncoding RNAs in Gastrointestinal Cancers. *Int. J. Mol. Sci.* **2022**, *23*, 930. [[CrossRef](#)] [[PubMed](#)]
54. Zhang, H.; Xing, J.; Dai, Z.; Wang, D.; Tang, D. Exosomes: The key of sophisticated cell-cell communication and targeted metastasis in pancreatic cancer. *Cell Commun. Signal* **2022**, *20*, 9. [[CrossRef](#)] [[PubMed](#)]
55. Rizk, N.I.; Abulsoud, A.I.; Kamal, M.M.; Kassem, D.H.; Hamdy, N.M. Exosomal-long non-coding RNAs journey in colorectal cancer: Evil and goodness faces of key players. *Life Sci.* **2022**, *292*, 120325. [[CrossRef](#)]
56. Cione, E.; Cannataro, R.; Gallelli, L.; De Sarro, G.; Caroleo, M.C. Exosome microRNAs in Metabolic Syndrome as Tools for the Early Monitoring of Diabetes and Possible Therapeutic Options. *Pharmaceuticals* **2021**, *14*, 1257. [[CrossRef](#)] [[PubMed](#)]
57. Tominaga, N. Anti-Cancer Role and Therapeutic Potential of Extracellular Vesicles. *Cancers* **2021**, *13*, 6303. [[CrossRef](#)]
58. Teles, R.H.G.; Yano, R.S.; Villarinho, N.J.; Yamagata, A.S.; Jaeger, R.G.; Meybohm, P.; Burek, M.; Freitas, V.M. Advances in Breast Cancer Management and Extracellular Vesicle Research, a Bibliometric Analysis. *Curr. Oncol.* **2021**, *28*, 4504–4520. [[CrossRef](#)] [[PubMed](#)]
59. Zou, J.; Peng, H.; Liu, Y. The Roles of Exosomes in Immunoregulation and Autoimmune Thyroid Diseases. *Front. Immunol.* **2021**, *12*, 757674. [[CrossRef](#)]
60. Khodamoradi, K.; Golan, R.; Dullea, A.; Ramasamy, R. Exosomes as Potential Biomarkers for Erectile Dysfunction, Varicocele, and Testicular Injury. *Sex Med. Rev.* **2022**, *10*, 311–322. [[CrossRef](#)] [[PubMed](#)]
61. Zhang, W.; Wang, Q.; Yang, Y.; Zhou, S.; Zhang, P.; Feng, T. The role of exosomal lncRNAs in cancer biology and clinical management. *Exp. Mol. Med.* **2021**, *53*, 1669–1673. [[CrossRef](#)] [[PubMed](#)]
62. Chen, S.; He, R.; He, B.; Xu, L.; Zhang, S. Potential Roles of Exosomal lncRNAs in the Intestinal Mucosal Immune Barrier. *J. Immunol. Res.* **2021**, *2021*, 7183136. [[CrossRef](#)] [[PubMed](#)]
63. Chen, Q.; Xie, X. Association of Exosomal miR-210 with Signaling Pathways Implicated in Lung Cancer. *Genes* **2021**, *12*, 1248. [[CrossRef](#)] [[PubMed](#)]
64. Heydari, R.; Abdollahpour-Alitappeh, M.; Shekari, F.; Meyfour, A. Emerging Role of Extracellular Vesicles in Biomarking the Gastrointestinal Diseases. *Expert. Rev. Mol. Diagn.* **2021**, *21*, 939–962. [[CrossRef](#)] [[PubMed](#)]
65. Ghafouri-Fard, S.; Niazi, V.; Hussien, B.M.; Omrani, M.D.; Taheri, M.; Basiri, A. The Emerging Role of Exosomes in the Treatment of Human Disorders with a Special Focus on Mesenchymal Stem Cells-Derived Exosomes. *Front. Cell Dev. Biol.* **2021**, *9*, 653296. [[CrossRef](#)]
66. Cricri, G.; Bellucci, L.; Montini, G.; Collino, F. Urinary Extracellular Vesicles: Uncovering the Basis of the Pathological Processes in Kidney-Related Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 6507. [[CrossRef](#)]
67. Alhamwe, A.B.; Potaczek, D.P.; Miethel, S.; Alhamdan, F.; Hintz, L.; Magomedov, A.; Garn, H. Extracellular Vesicles and Asthma—More Than Just a Co-Existence. *Int. J. Mol. Sci.* **2021**, *22*, 4984. [[CrossRef](#)]
68. Gysler, S.M.; Drapkin, R. Tumor innervation: Peripheral nerves take control of the tumor microenvironment. *J. Clin. Investig.* **2021**, *131*, e147276. [[CrossRef](#)]
69. Qiu, Y.; Li, P.; Zhang, Z.; Wu, M. Insights into Exosomal Non-Coding RNAs Sorting Mechanism and Clinical Application. *Front. Oncol.* **2021**, *11*, 664904. [[CrossRef](#)]
70. Albacete-Albacete, L.; Sánchez-Álvarez, M.; Del Pozo, M.A. Extracellular Vesicles: An Emerging Mechanism Governing the Secretion and Biological Roles of Tenascin-C. *Front. Immunol.* **2021**, *12*, 671485. [[CrossRef](#)]
71. Wu, H.; Fu, M.; Liu, J.; Chong, W.; Fang, Z.; Du, F.; Liu, Y.; Shang, L.; Li, L. The role and application of small extracellular vesicles in gastric cancer. *Mol. Cancer* **2021**, *20*, 71. [[CrossRef](#)] [[PubMed](#)]
72. Sun, Y.F.; Pi, J.; Xu, J.F. Emerging Role of Exosomes in Tuberculosis: From Immunity Regulations to Vaccine and Immunotherapy. *Front. Immunol.* **2021**, *12*, 628973. [[CrossRef](#)] [[PubMed](#)]
73. Perocheau, D.; Touramanidou, L.; Gurung, S.; Gissen, P.; Baruteau, J. Clinical applications for exosomes: Are we there yet? *Br. J. Pharmacol.* **2021**, *178*, 2375–2392. [[CrossRef](#)] [[PubMed](#)]
74. Jafari, A.; Babajani, A.; Abdollahpour-Alitappeh, M.; Ahmadi, N.; Rezaei-Tavirani, M. Exosomes and cancer: From molecular mechanisms to clinical applications. *Med. Oncol.* **2021**, *38*, 45. [[CrossRef](#)]
75. Casari, I.; Howard, J.A.; Robless, E.E.; Falasca, M. Exosomal integrins and their influence on pancreatic cancer progression and metastasis. *Cancer Lett.* **2021**, *507*, 124–134. [[CrossRef](#)]

76. Lizarraga-Valderrama, L.R.; Sheridan, G.K. Extracellular vesicles and intercellular communication in the central nervous system. *FEBS Lett.* **2021**, *595*, 1391–1410. [[CrossRef](#)]
77. Esfandyari, S.; Elkafas, H.; Chugh, R.M.; Park, H.S.; Navarro, A.; Al-Hendy, A. Exosomes as Biomarkers for Female Reproductive Diseases Diagnosis and Therapy. *Int. J. Mol. Sci.* **2021**, *22*, 2165. [[CrossRef](#)]
78. Saludas, L.; Oliveira, C.C.; Roncal, C.; Ruiz-Villalba, A.; Prósper, F.; Garbayo, E.; Blanco-Prieto, M.J. Extracellular Vesicle-Based Therapeutics for Heart Repair. *Nanomaterials* **2021**, *11*, 570. [[CrossRef](#)]
79. Wei, X.; Shi, Y.; Dai, Z.; Wang, P.; Meng, X.; Yin, B. Underlying metastasis mechanism and clinical application of exosomal circular RNA in tumors (Review). *Int. J. Oncol.* **2021**, *58*, 289–297. [[CrossRef](#)]
80. Makarova, J.; Turchinovich, A.; Shkurnikov, M.; Tonevitsky, A. Extracellular miRNAs and Cell-Cell Communication: Problems and Prospects. *Trends Biochem. Sci.* **2021**, *46*, 640–651. [[CrossRef](#)]
81. Amintas, S.; Vendrely, V.; Dupin, C.; Buscail, L.; Laurent, C.; Bournet, B.; Merlio, J.P.; Bedel, A.; Moreau-Gaudry, F.; Boutin, J.; et al. Next-Generation Cancer Biomarkers: Extracellular Vesicle DNA as a Circulating Surrogate of Tumor DNA. *Front. Cell Dev. Biol.* **2021**, *8*, 622048. [[CrossRef](#)]
82. Røsand, Ø.; Høydal, M.A. Cardiac Exosomes in Ischemic Heart Disease—A Narrative Review. *Diagnostics* **2021**, *11*, 269. [[CrossRef](#)] [[PubMed](#)]
83. Fareez, I.M.; Seng, W.Y.; Zaki, R.M.; Shafiq, A.; Izwan, I.M. Molecular and Epigenetic Basis of Extracellular Vesicles Cell Repair Phenotypes in Targeted Organ-specific Regeneration. *Curr. Mol. Med.* **2022**, *22*, 132–150. [[CrossRef](#)]
84. Marostica, G.; Gelibter, S.; Gironi, M.; Nigro, A.; Furlan, R. Extracellular Vesicles in Neuroinflammation. *Front. Cell Dev. Biol.* **2021**, *8*, 623039. [[CrossRef](#)] [[PubMed](#)]
85. Tan, K.L.; Chia, W.C.; How, C.W.; Tor, Y.S.; Show, P.L.; Looi, Q.H.D.; Foo, J.B. Benchtop Isolation and Characterisation of Small Extracellular Vesicles from Human Mesenchymal Stem Cells. *Mol. Biotechnol.* **2021**, *63*, 780–791. [[CrossRef](#)]
86. Poon, I.K.H.; Parkes, M.A.F.; Jiang, L.; Atkin-Smith, G.K.; Tixeira, R.; Gregory, C.D.; Ozkocak, D.C.; Rutter, S.F.; Caruso, S.; Santavanond, J.P.; et al. Moving beyond size and phosphatidylserine exposure: Evidence for a diversity of apoptotic cell-derived extracellular vesicles in vitro. *J. Extracell. Vesicles* **2019**, *8*, 1608786. [[CrossRef](#)] [[PubMed](#)]
87. Matsumura, S.; Minamisawa, T.; Suga, K.; Kishita, H.; Akagi, T.; Ichiki, T.; Ichikawa, Y.; Shiba, K. Subtypes of tumour cell-derived small extracellular vesicles having differently externalized phosphatidylserine. *J. Extracell. Vesicles* **2019**, *8*, 1579541. [[CrossRef](#)]
88. Oyarce, K.; Cepeda, M.Y.; Lagos, R.; Garrido, C.; Vega-Letter, A.M.; Garcia-Robles, M.; Luz-Crawford, P.; Elizondo-Vega, R. Neuroprotective and Neurotoxic Effects of Glial-Derived Exosomes. *Front. Cell Neurosci.* **2022**, *16*, 920686. [[CrossRef](#)]
89. Hu, C.; Jiang, W.; Lv, M.; Fan, S.; Lu, Y.; Wu, Q.; Pi, J. Potentiality of Exosomal Proteins as Novel Cancer Biomarkers for Liquid Biopsy. *Front. Immunol.* **2022**, *13*, 792046. [[CrossRef](#)]
90. Bano, R.; Ahmad, F.; Mohsin, M. A perspective on the isolation and characterization of extracellular vesicles from different biofluids. *RSC Adv.* **2021**, *11*, 19598–19615. [[CrossRef](#)]
91. Gurunathan, S.; Kang, M.H.; Song, H.; Kim, N.H.; Kim, J.H. The role of extracellular vesicles in animal reproduction and diseases. *J. Anim. Sci. Biotechnol.* **2022**, *13*, 62. [[CrossRef](#)] [[PubMed](#)]
92. Kawaguchi, N.; Nakanishi, T. Stem Cell Studies in Cardiovascular Biology and Medicine: A Possible Key Role of Macrophages. *Biology* **2022**, *11*, 122. [[CrossRef](#)] [[PubMed](#)]
93. Pulliam, L.; Sun, B.; Mustapic, M.; Chawla, S.; Kapogiannis, D. Plasma neuronal exosomes serve as biomarkers of cognitive impairment in HIV infection and Alzheimer’s disease. *J. Neurovirol.* **2019**, *25*, 702–709. [[CrossRef](#)]
94. Salomon, C.; Nuzhat, Z.; Dixon, C.L.; Menon, R. Placental Exosomes During Gestation: Liquid Biopsies Carrying Signals for the Regulation of Human Parturition. *Curr. Pharm. Des.* **2018**, *24*, 974–982. [[CrossRef](#)]
95. Carnino, J.M.; Lee, H. Extracellular vesicles in respiratory disease. *Adv. Clin. Chem.* **2022**, *108*, 105–127. [[CrossRef](#)] [[PubMed](#)]
96. Pathania, A.S.; Prathipati, P.; Challagundla, K.B. New insights into exosome mediated tumor-immune escape: Clinical perspectives and therapeutic strategies. *Biochim. Biophys. Acta Rev. Cancer* **2021**, *1876*, 188624. [[CrossRef](#)]
97. Wu, J.; Xie, Q.; Liu, Y.; Gao, Y.; Qu, Z.; Mo, L.; Xu, Y.; Chen, R.; Shi, L. A Small Vimentin-Binding Molecule Blocks Cancer Exosome Release and Reduces Cancer Cell Mobility. *Front. Pharmacol.* **2021**, *12*, 627394. [[CrossRef](#)]
98. Grieco, G.E.; Fignani, D.; Formichi, C.; Nigi, L.; Licata, G.; Maccora, C.; Brusco, N.; Sebastiani, G.; Dotta, F. Extracellular Vesicles in Immune System Regulation and Type 1 Diabetes: Cell-to-Cell Communication Mediators, Disease Biomarkers, and Promising Therapeutic Tools. *Front. Immunol.* **2021**, *12*, 682948. [[CrossRef](#)]
99. Burillo, J.; Fernández-Rhodes, M.; Piquero, M.; López-Alvarado, P.; Menéndez, J.C.; Jiménez, B.; González-Blanco, C.; Marqués, P.; Guillén, C.; Benito, M. Human amylin aggregates release within exosomes as a protective mechanism in pancreatic β cells: Pancreatic β -hippocampal cell communication. *Biochim. Biophys. Acta Mol. Cell Res.* **2021**, *1868*, 118971. [[CrossRef](#)]
100. Wang, C.A.; Tsai, S.J. Regulation of lymphangiogenesis by extracellular vesicles in cancer metastasis. *Exp. Biol. Med.* **2021**, *246*, 2048–2056. [[CrossRef](#)]
101. Kim, K.S.; Park, J.I.; Oh, N.; Cho, H.J.; Park, J.H.; Park, K.S. ELK3 expressed in lymphatic endothelial cells promotes breast cancer progression and metastasis through exosomal miRNAs. *Sci. Rep.* **2019**, *9*, 8418. [[CrossRef](#)]
102. Wang, D.; Zhang, W.; Zhang, C.; Wang, L.; Chen, H.; Xu, J. Exosomal non-coding RNAs have a significant effect on tumor metastasis. *Mol. Ther. Nucleic Acids* **2022**, *29*, 16–35. [[CrossRef](#)] [[PubMed](#)]

103. Monti, M.; Lunardini, S.; Magli, I.A.; Campi, R.; Primiceri, G.; Berardinelli, F.; Amparore, D.; Terracciano, D.; Lucarelli, G.; Schips, L.; et al. Micro-RNAs Predict Response to Systemic Treatments in Metastatic Renal Cell Carcinoma Patients: Results from a Systematic Review of the Literature. *Biomedicines* **2022**, *10*, 1287. [[CrossRef](#)] [[PubMed](#)]
104. Yang, M.; Sun, M.; Zhang, H. The Interaction Between Epigenetic Changes, EMT, and Exosomes in Predicting Metastasis of Colorectal Cancers (CRC). *Front. Oncol.* **2022**, *12*, 879848. [[CrossRef](#)]
105. Khera, A.; Alajangi, H.K.; Khajuria, A.; Barnwal, R.P.; Kumar, S.; Singh, G. Highlighting the potential role of Exosomes as the targeted nano-therapeutic carrier in metastatic breast cancer. *Curr. Drug Deliv.* **2022**; *in press*. [[CrossRef](#)]
106. Tămaş, F.; Bălaşa, R.; Manu, D.; Gyorki, G.; Chinezu, R.; Tămaş, C.; Bălaşa, A. The Importance of Small Extracellular Vesicles in the Cerebral Metastatic Process. *Int. J. Mol. Sci.* **2022**, *23*, 1449. [[CrossRef](#)] [[PubMed](#)]
107. Sunami, Y.; Häußler, J.; Zourelidis, A.; Kleeff, J. Cancer-Associated Fibroblasts and Tumor Cells in Pancreatic Cancer Microenvironment and Metastasis: Paracrine Regulators, Reciprocation and Exosomes. *Cancers* **2022**, *14*, 744. [[CrossRef](#)]
108. Bai, S.; Wei, Y.; Liu, R.; Xu, R.; Xiang, L.; Du, J. Role of tumour-derived exosomes in metastasis. *Biomed. Pharmacother.* **2022**, *147*, 112657. [[CrossRef](#)]
109. Zhou, H.; He, X.; He, Y.; Ou, C.; Cao, P. Exosomal circRNAs: Emerging Players in Tumor Metastasis. *Front. Cell Dev. Biol.* **2021**, *9*, 786224. [[CrossRef](#)]
110. Pascual-Antón, L.; Cardeñes, B.; Sainz de la Cuesta, R.; González-Cortijo, L.; López-Cabrera, M.; Cabañas, C.; Sandoval, P. Mesothelial-to-Mesenchymal Transition and Exosomes in Peritoneal Metastasis of Ovarian Cancer. *Int. J. Mol. Sci.* **2021**, *22*, 11496. [[CrossRef](#)]
111. Shen, B.; Sun, K. Exosomal circular RNAs: A new frontier in the metastasis of digestive system tumors. *Oncol. Lett.* **2021**, *22*, 826. [[CrossRef](#)]
112. Singh, M.; Agarwal, S.; Agarwal, V.; Mall, S.; Pancham, P.; Mani, S. Current theranostic approaches for metastatic cancers through hypoxia-induced exosomal packaged cargo. *Life Sci.* **2021**, *286*, 120017. [[CrossRef](#)] [[PubMed](#)]
113. Yang, X.; Zhang, Y.; Zhang, Y.; Zhang, S.; Qiu, L.; Zhuang, Z.; Wei, M.; Deng, X.; Wang, Z.; Han, J. The Key Role of Exosomes on the Pre-metastatic Niche Formation in Tumors. *Front. Mol. Biosci.* **2021**, *8*, 703640. [[CrossRef](#)] [[PubMed](#)]
114. Mkhobongo, B.; Chandran, R.; Abrahamse, H. The Role of Melanoma Cell-Derived Exosomes (MTEX) and Photodynamic Therapy (PDT) within a Tumor Microenvironment. *Int. J. Mol. Sci.* **2021**, *22*, 9726. [[CrossRef](#)] [[PubMed](#)]
115. Chen, H.; Chengalvala, V.; Hu, H.; Sun, D. Tumor-derived exosomes: Nanovesicles made by cancer cells to promote cancer metastasis. *Acta Pharm. Sin. B* **2021**, *11*, 2136–2149. [[CrossRef](#)] [[PubMed](#)]
116. Jiang, C.; Zhang, N.; Hu, X.; Wang, H. Tumor-associated exosomes promote lung cancer metastasis through multiple mechanisms. *Mol. Cancer* **2021**, *20*, 117. [[CrossRef](#)]
117. Seibold, T.; Waldenmaier, M.; Seufferlein, T.; Eiseler, T. Small Extracellular Vesicles and Metastasis-Blame the Messenger. *Cancers* **2021**, *13*, 4380. [[CrossRef](#)]
118. Zhao, L.; Ma, X.; Yu, J. Exosomes and organ-specific metastasis. *Mol. Ther. Methods Clin. Dev.* **2021**, *22*, 133–147. [[CrossRef](#)]
119. Storti, G.; Scioli, M.G.; Kim, B.S.; Terriaca, S.; Fiorelli, E.; Orlandi, A.; Cervelli, V. Mesenchymal Stem Cells in Adipose Tissue and Extracellular Vesicles in Ovarian Cancer Patients: A Bridge toward Metastatic Diffusion or a New Therapeutic Opportunity? *Cells* **2021**, *10*, 2117. [[CrossRef](#)]
120. Zarin, B.; Rafiee, L.; Daneshpajouhnejad, P.; Haghjooy Javanmard, S. A review on the role of CAFs and CAF-derived exosomes in progression and metastasis of digestive system cancers. *Tumour Biol.* **2021**, *43*, 141–157. [[CrossRef](#)]
121. Yin, L.; Liu, X.; Shao, X.; Feng, T.; Xu, J.; Wang, Q.; Hua, S. The role of exosomes in lung cancer metastasis and clinical applications: An updated review. *J. Transl. Med.* **2021**, *19*, 312. [[CrossRef](#)]
122. Chen, X.; Wang, H.; Huang, Y.; Chen, Y.; Chen, C.; Zhuo, W.; Teng, L. Comprehensive Roles and Future Perspectives of Exosomes in Peritoneal Metastasis of Gastric Cancer. *Front. Oncol.* **2021**, *11*, 684871. [[CrossRef](#)] [[PubMed](#)]
123. Balaji, S.; Kim, U.; Muthukkaruppan, V.; Vanniarajan, A. Emerging role of tumor microenvironment derived exosomes in therapeutic resistance and metastasis through epithelial-to-mesenchymal transition. *Life Sci.* **2021**, *280*, 119750. [[CrossRef](#)] [[PubMed](#)]
124. Gao, J.; Li, S.; Xu, Q.; Zhang, X.; Huang, M.; Dai, X.; Liu, L. Exosomes Promote Pre-Metastatic Niche Formation in Gastric Cancer. *Front. Oncol.* **2021**, *11*, 652378. [[CrossRef](#)] [[PubMed](#)]
125. Al-Humaidi, R.B.; Fayed, B.; Sharif, S.I.; Noreddin, A.; Soliman, S.S.M. Role of Exosomes in Breast Cancer Management: Evidence-Based Review. *Curr. Cancer Drug Targets* **2021**, *21*, 666–675. [[CrossRef](#)] [[PubMed](#)]
126. Tan, Y.; Luo, X.; Lv, W.; Hu, W.; Zhao, C.; Xiong, M.; Yi, Y.; Wang, D.; Wang, Y.; Wang, H.; et al. Tumor-derived exosomal components: The multifaceted roles and mechanisms in breast cancer metastasis. *Cell Death Dis.* **2021**, *12*, 547. [[CrossRef](#)] [[PubMed](#)]
127. Gao, Z.; Pang, B.; Li, J.; Gao, N.; Fan, T.; Li, Y. Emerging Role of Exosomes in Liquid Biopsy for Monitoring Prostate Cancer Invasion and Metastasis. *Front. Cell Dev. Biol.* **2021**, *9*, 679527. [[CrossRef](#)]
128. Wang, X.; Zhou, Y.; Ding, K. Roles of exosomes in cancer chemotherapy resistance, progression, metastasis and immunity, and their clinical applications (Review). *Int. J. Oncol.* **2021**, *59*, 44. [[CrossRef](#)]
129. Danac, J.M.C.; Uy, A.G.G.; Garcia, R.L. Exosomal microRNAs in colorectal cancer: Overcoming barriers of the metastatic cascade (Review). *Int. J. Mol. Med.* **2021**, *47*, 112. [[CrossRef](#)]
130. Akoto, T.; Saini, S. Role of Exosomes in Prostate Cancer Metastasis. *Int. J. Mol. Sci.* **2021**, *22*, 3528. [[CrossRef](#)]

131. Fu, C.; Zhang, Q.; Wang, A.; Yang, S.; Jiang, Y.; Bai, L.; Wei, Q. EWI-2 controls nucleocytoplasmic shuttling of EGFR signaling molecules and miRNA sorting in exosomes to inhibit prostate cancer cell metastasis. *Mol. Oncol.* **2021**, *15*, 1543–1565. [[CrossRef](#)]
132. Peng, L.; Wang, D.; Han, Y.; Huang, T.; He, X.; Wang, J.; Ou, C. Emerging Role of Cancer-Associated Fibroblasts-Derived Exosomes in Tumorigenesis. *Front. Immunol.* **2022**, *12*, 795372. [[CrossRef](#)]
133. Tang, L.B.; Ma, S.X.; Chen, Z.H.; Huang, Q.Y.; Wu, L.Y.; Wang, Y.; Zhao, R.C.; Xiong, L.X. Exosomal microRNAs: Pleiotropic Impacts on Breast Cancer Metastasis and Their Clinical Perspectives. *Biology* **2021**, *10*, 307. [[CrossRef](#)] [[PubMed](#)]
134. Guo, Y.; Ji, X.; Liu, J.; Fan, D.; Zhou, Q.; Chen, C.; Wang, W.; Wang, G.; Wang, H.; Yuan, W.; et al. Effects of exosomes on pre-metastatic niche formation in tumors. *Mol. Cancer* **2019**, *18*, 39. [[CrossRef](#)] [[PubMed](#)]
135. Jia, Z.; Jia, J.; Yao, L.; Li, Z. Crosstalk of Exosomal Non-Coding RNAs in The Tumor Microenvironment: Novel Frontiers. *Front. Immunol.* **2022**, *13*, 900155. [[CrossRef](#)]
136. Su, M.T.; Kumata, S.; Endo, S.; Okada, Y.; Takai, T. LILRB4 promotes tumor metastasis by regulating MDSCs and inhibiting miR-1 family miRNAs. *Oncoimmunology* **2022**, *11*, 2060907. [[CrossRef](#)] [[PubMed](#)]
137. Sendi, H.; Yazdimamaghani, M.; Hu, M.; Sultanpuram, N.; Wang, J.; Moody, A.S.; McCabe, E.; Zhang, J.; Graboski, A.; Li, L.; et al. Nanoparticle Delivery of miR-122 Inhibits Colorectal Cancer Liver Metastasis. *Cancer Res.* **2022**, *82*, 105–113. [[CrossRef](#)] [[PubMed](#)]
138. Yang, S.J.; Wang, D.D.; Zhong, S.L.; Chen, W.Q.; Wang, F.L.; Zhang, J.; Xu, W.X.; Xu, D.; Zhang, Q.; Li, J.; et al. Tumor-derived exosomal circPSMA1 facilitates the tumorigenesis, metastasis, and migration in triple-negative breast cancer (TNBC) through miR-637/Akt1/ β -catenin (cyclin D1) axis. *Cell Death Dis.* **2021**, *12*, 420. [[CrossRef](#)]
139. Chen, S.; Chen, X.; Qiu, J.; Chen, P.; Han, X.; Wu, Y.; Zhuang, J.; Yang, M.; Wu, N.; et al. Exosomes derived from retinoblastoma cells enhance tumour deterioration by infiltrating the microenvironment. *Oncol. Rep.* **2021**, *45*, 278–290. [[CrossRef](#)]
140. Moradi-Chaleshtori, M.; Bandehpour, M.; Heidari, N.; Mohammadi-Yeganeh, S.; Mahmoud Hashemi, S. Exosome-mediated miR-33 transfer induces M1 polarization in mouse macrophages and exerts antitumor effect in 4T1 breast cancer cell line. *Int. Immunopharmacol.* **2021**, *90*, 107198. [[CrossRef](#)]
141. Zhao, M.; Zhuang, A.; Fang, Y. Cancer-Associated Fibroblast-Derived Exosomal miRNA-320a Promotes Macrophage M2 Polarization In Vitro by Regulating PTEN/PI3K γ Signaling in Pancreatic Cancer. *J. Oncol.* **2022**, *2022*, 9514697. [[CrossRef](#)]
142. Qi, M.; Xia, Y.; Wu, Y.; Zhang, Z.; Wang, X.; Lu, L.; Dai, C.; Song, Y.; Xu, K.; Ji, W.; et al. Lin28B-high breast cancer cells promote immune suppression in the lung pre-metastatic niche via exosomes and support cancer progression. *Nat. Commun.* **2022**, *13*, 897. [[CrossRef](#)] [[PubMed](#)]
143. Yoshida, K.; Yokoi, A.; Kato, T.; Ochiya, T.; Yamamoto, Y. The clinical impact of intra- and extracellular miRNAs in ovarian cancer. *Cancer Sci.* **2020**, *111*, 3435–3444. [[CrossRef](#)] [[PubMed](#)]
144. Yang, C.; Kim, H.S.; Song, G.; Lim, W. The potential role of exosomes derived from ovarian cancer cells for diagnostic and therapeutic approaches. *J. Cell Physiol.* **2019**, *234*, 21493–21503. [[CrossRef](#)] [[PubMed](#)]
145. Wu, X.G.; Zhou, C.F.; Zhang, Y.M.; Yan, R.M.; Wei, W.F.; Chen, X.J.; Yi, H.Y.; Liang, L.J.; Fan, L.S.; Liang, L.; et al. Cancer-derived exosomal miR-221-3p promotes angiogenesis by targeting THBS2 in cervical squamous cell carcinoma. *Angiogenesis* **2019**, *22*, 397–410. [[CrossRef](#)]
146. Chen, K.; Wang, Q.; Liu, X.; Wang, F.; Yang, Y.; Tian, X. Hypoxic pancreatic cancer derived exosomal miR-30b-5p promotes tumor angiogenesis by inhibiting GJA1 expression. *Int. J. Biol. Sci.* **2022**, *18*, 1220–1237. [[CrossRef](#)]
147. Duréndez-Sáez, E.; Torres-Martínez, S.; Calabuig-Fariñas, S.; Meri-Abad, M.; Ferrero-Gimeno, M.; Camps, C. Exosomal microRNAs in non-small cell lung cancer. *Transl. Cancer Res.* **2021**, *10*, 3128–3139. [[CrossRef](#)]
148. Li, C.; Zhou, T.; Chen, J.; Li, R.; Chen, H.; Luo, S.; Chen, D.; Cai, C.; Li, W. The role of Exosomal miRNAs in cancer. *J. Transl. Med.* **2022**, *20*, 6. [[CrossRef](#)]
149. Xu, J.L.; Xu, W.X.; Tang, J.H. Exosomal circRNAs: A new communication method in cancer. *Am. J. Transl. Res.* **2021**, *13*, 12913–12928.
150. Tominaga, N.; Kosaka, N.; Ono, M.; Katsuda, T.; Yoshioka, Y.; Tamura, K.; Lötvall, J.; Nakagama, H.; Ochiya, T. Brain metastatic cancer cells release microRNA-181c-containing extracellular vesicles capable of destructing blood-brain barrier. *Nat. Commun.* **2015**, *6*, 6716. [[CrossRef](#)]
151. Geng, S.; Tu, S.; Bai, Z.; Geng, Y. Exosomal lncRNA LINC01356 Derived from Brain Metastatic Non-small-Cell Lung Cancer Cells Remodels the Blood-Brain Barrier. *Front. Oncol.* **2022**, *12*, 825899. [[CrossRef](#)]
152. Curtaz, C.J.; Reifschläger, L.; Strähle, L.; Feldheim, J.; Feldheim, J.J.; Schmitt, C.; Kiesel, M.; Herbert, S.L.; Wöckel, A.; Meybohm, P.; et al. Analysis of microRNAs in Exosomes of Breast Cancer Patients in Search of Molecular Prognostic Factors in Brain Metastases. *Int. J. Mol. Sci.* **2022**, *23*, 3683. [[CrossRef](#)] [[PubMed](#)]
153. Busatto, S.; Morad, G.; Guo, P.; Moses, M.A. The role of extracellular vesicles in the physiological and pathological regulation of the blood-brain barrier. *FASEB Bioadv.* **2021**, *3*, 665–675. [[CrossRef](#)] [[PubMed](#)]
154. Wu, D.; Deng, S.; Li, L.; Liu, T.; Zhang, T.; Li, J.; Yu, Y.; Xu, Y. TGF- β 1-mediated exosomal lnc-MMP2-2 increases blood-brain barrier permeability via the miRNA-1207-5p/EPB41L5 axis to promote non-small cell lung cancer brain metastasis. *Cell Death Dis.* **2021**, *12*, 721. [[CrossRef](#)]
155. Yokoi, A.; Yoshioka, Y.; Yamamoto, Y.; Ishikawa, M.; Ikeda, S.I.; Kato, T.; Kiyono, T.; Takeshita, F.; Kajiyama, H.; Kikkawa, F.; et al. Malignant extracellular vesicles carrying MMP1 mRNA facilitate peritoneal dissemination in ovarian cancer. *Nat. Commun.* **2017**, *8*, 14470. [[CrossRef](#)]

156. Wang, G.; Xie, L.; Li, B.; Sang, W.; Yan, J.; Li, J.; Tian, H.; Li, W.; Zhang, Z.; Tian, Y.; et al. A nanounit strategy reverses immune suppression of exosomal PD-L1 and is associated with enhanced ferroptosis. *Nat. Commun.* **2021**, *12*, 5733. [[CrossRef](#)] [[PubMed](#)]
157. Xu, Z.; Tsai, H.I.; Xiao, Y.; Wu, Y.; Su, D.; Yang, M.; Zha, H.; Yan, F.; Liu, X.; Cheng, F.; et al. Engineering Programmed Death Ligand-1/Cytotoxic T-Lymphocyte-Associated Antigen-4 Dual-Targeting Nanovesicles for Immunosuppressive Therapy in Transplantation. *ACS Nano* **2020**, *14*, 7959–7969. [[CrossRef](#)]
158. Xie, L.; Li, J.; Wang, G.; Sang, W.; Xu, M.; Li, W.; Yan, J.; Li, B.; Zhang, Z.; Zhao, Q.; et al. Phototheranostic Metal-Phenolic Networks with Antiexosomal PD-L1 Enhanced Ferroptosis for Synergistic Immunotherapy. *J. Am. Chem. Soc.* **2022**, *144*, 787–797. [[CrossRef](#)]
159. Chen, J.; Song, Y.; Miao, F.; Chen, G.; Zhu, Y.; Wu, N.; Pang, L.; Chen, Z.; Chen, X. PDL1-positive exosomes suppress antitumor immunity by inducing tumor-specific CD8⁺ T cell exhaustion during metastasis. *Cancer Sci.* **2021**, *112*, 3437–3454. [[CrossRef](#)]
160. Liu, N.; Zhang, J.; Yin, M.; Liu, H.; Zhang, X.; Li, J.; Yan, B.; Guo, Y.; Zhou, J.; Tao, J.; et al. Inhibition of xCT suppresses the efficacy of anti-PD-1/L1 melanoma treatment through exosomal PD-L1-induced macrophage M2 polarization. *Mol. Ther.* **2021**, *29*, 2321–2334. [[CrossRef](#)]
161. Shu, S.; Matsuzaki, J.; Want, M.Y.; Conway, A.; Benjamin-Davalos, S.; Allen, C.L.; Koroleva, M.; Battaglia, S.; Odunsi, A.; Minderman, H.; et al. An Immunosuppressive Effect of Melanoma-derived Exosomes on NY-ESO-1 Antigen-specific Human CD8⁺ T Cells is Dependent on IL-10 and Independent of BRAF^{V600E} Mutation in Melanoma Cell Lines. *Immunol. Investig.* **2020**, *49*, 744–757. [[CrossRef](#)]
162. Chen, G.; Huang, A.C.; Zhang, W.; Zhang, G.; Wu, M.; Xu, W.; Yu, Z.; Yang, J.; Wang, B.; Sun, H.; et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature* **2018**, *560*, 382–386. [[CrossRef](#)] [[PubMed](#)]
163. Rupareliya, C.; Naqvi, S.; Jani, V.B. Acute Inflammatory Demyelinating Polyneuroradiculopathy with Ipilimumab in Metastatic Melanoma: A Case Report and Review of Literature. *Cureus* **2017**, *9*, e1310. [[CrossRef](#)] [[PubMed](#)]
164. Mastoraki, A.; Gkiala, A.; Theodoroleas, G.; Mouchtouri, E.; Strimpakos, A.; Papagiannopoulou, D.; Schizas, D. Metastatic malignant melanoma of the breast: Report of a case and review of the literature. *Folia. Med.* **2022**, *64*, 354–358. [[CrossRef](#)] [[PubMed](#)]
165. Gracia-Hernandez, M.; Munoz, Z.; Villagra, A. Enhancing Therapeutic Approaches for Melanoma Patients Targeting Epigenetic Modifiers. *Cancers* **2021**, *13*, 6180. [[CrossRef](#)] [[PubMed](#)]
166. Ma, B.; Anandasabapathy, N. Immune Checkpoint Blockade and Skin Toxicity Pathogenesis. *J. Investig. Dermatol.* **2022**, *142*, 951–959. [[CrossRef](#)] [[PubMed](#)]
167. Dietz, H.; Weinmann, S.C.; Salama, A.K. Checkpoint Inhibitors in Melanoma Patients with Underlying Autoimmune Disease. *Cancer Manag. Res.* **2021**, *13*, 8199–8208. [[CrossRef](#)] [[PubMed](#)]
168. Sun, Y.M.; Li, W.; Chen, Z.Y.; Wang, Y. Risk of Pneumonitis Associated with Immune Checkpoint Inhibitors in Melanoma: A Systematic Review and Network Meta-Analysis. *Front. Oncol.* **2021**, *11*, 651553. [[CrossRef](#)]
169. Zawit, M.; Swami, U.; Awada, H.; Arnouk, J.; Milhem, M.; Zakharia, Y. Current status of intralesional agents in treatment of malignant melanoma. *Ann. Transl. Med.* **2021**, *9*, 1038. [[CrossRef](#)]
170. Sakellariou, S.; Zouki, D.N.; Ziogas, D.C.; Pouloudi, D.; Gogas, H.; Delladetsima, I. Granulomatous colitis in a patient with metastatic melanoma under immunotherapy: A case report and literature review. *BMC Gastroenterol.* **2021**, *21*, 227. [[CrossRef](#)]
171. Li, J.H.; Huang, L.J.; Zhou, H.L.; Shan, Y.M.; Chen, F.M.; Lehto, V.P.; Xu, W.J.; Luo, L.Q.; Yu, H.J. Engineered nanomedicines block the PD-1/PD-L1 axis for potentiated cancer immunotherapy. *Acta Pharmacol. Sin.* **2022**, *43*, 2749–2758. [[CrossRef](#)]
172. Archilla-Ortega, A.; Domuro, C.; Martin-Liberal, J.; Muñoz, P. Blockade of novel immune checkpoints and new therapeutic combinations to boost antitumor immunity. *J. Exp. Clin. Cancer Res.* **2022**, *41*, 62. [[CrossRef](#)] [[PubMed](#)]
173. Ye, L.; Zhu, Z.; Chen, X.; Zhang, H.; Huang, J.; Gu, S.; Zhao, X. The Importance of Exosomal PD-L1 in Cancer Progression and Its Potential as a Therapeutic Target. *Cells* **2021**, *10*, 3247. [[CrossRef](#)] [[PubMed](#)]
174. Palicelli, A.; Croci, S.; Bisagni, A.; Zanetti, E.; De Biase, D.; Melli, B.; Sanguedolce, F.; Ragazzi, M.; Zanelli, M.; Chaux, A.; et al. What Do We Have to Know about PD-L1 Expression in Prostate Cancer? A Systematic Literature Review. Part 3: PD-L1, Intracellular Signaling Pathways and Tumor Microenvironment. *Int. J. Mol. Sci.* **2021**, *22*, 12330. [[CrossRef](#)] [[PubMed](#)]
175. Awadasseid, A.; Wu, Y.; Zhang, W. Advance investigation on synthetic small-molecule inhibitors targeting PD-1/PD-L1 signaling pathway. *Life Sci.* **2021**, *282*, 119813. [[CrossRef](#)]
176. Xing, K.; Zhou, P.; Li, J.; Liu, M.; Zhang, W.E. Inhibitory Effect of PD-1/PD-L1 and Blockade Immunotherapy in Leukemia. *Comb. Chem. High Throughput Screen* **2021**, *25*, 1399–1410. [[CrossRef](#)]
177. Huang, H.W.; Chang, C.C.; Wang, C.S.; Lin, K.H. Association between Inflammation and Function of Cell Adhesion Molecules Influence on Gastrointestinal Cancer Development. *Cells* **2021**, *10*, 67. [[CrossRef](#)]
178. Han, J.; Xu, X.; Liu, Z.; Li, Z.; Wu, Y.; Zuo, D. Recent advances of molecular mechanisms of regulating PD-L1 expression in melanoma. *Int. Immunopharmacol.* **2020**, *88*, 106971. [[CrossRef](#)]
179. Guan, L.; Wu, B.; Li, T.; Beer, L.A.; Sharma, G.; Li, M.; Lee, C.N.; Liu, S.; Yang, C.; Huang, L.; et al. HRS phosphorylation drives immunosuppressive exosome secretion and restricts CD8⁺ T-cell infiltration into tumors. *Nat. Commun.* **2022**, *13*, 4078. [[CrossRef](#)]
180. Zhang, J.; Zhu, Y.; Guan, M.; Liu, Y.; Lv, M.; Zhang, C.; Zhang, H.; Zhang, Z. Isolation of circulating exosomes and identification of exosomal PD-L1 for predicting immunotherapy response. *Nanoscale* **2022**, *14*, 8995–9003. [[CrossRef](#)]
181. Shen, D.D.; Pang, J.R.; Bi, Y.P.; Zhao, L.F.; Li, Y.R.; Zhao, L.J.; Gao, Y.; Wang, B.; Wang, N.; Wei, L.; et al. LSD1 deletion decreases exosomal PD-L1 and restores T-cell response in gastric cancer. *Mol. Cancer* **2022**, *21*, 75. [[CrossRef](#)]

182. Turiello, R.; Capone, M.; Morretta, E.; Monti, M.C.; Madonna, G.; Azzaro, R.; Del Gaudio, P.; Simeone, E.; Sorrentino, A.; Ascierio, P.A.; et al. Exosomal CD73 from serum of patients with melanoma suppresses lymphocyte functions and is associated with therapy resistance to anti-PD-1 agents. *J. Immunother. Cancer* **2022**, *10*, e004043. [[CrossRef](#)] [[PubMed](#)]
183. Zhang, W.; Zhong, W.; Wang, B.; Yang, J.; Yang, J.; Yu, Z.; Qin, Z.; Shi, A.; Xu, W.; Zheng, C.; et al. ICAM-1-mediated adhesion is a prerequisite for exosome-induced T cell suppression. *Dev. Cell* **2022**, *57*, 329–343.e7. [[CrossRef](#)] [[PubMed](#)]
184. Zanello, A.; Vautrot, V.; Aubin, F.; Avoscan, L.; Samimi, M.; Garrido, C.; Gobbo, J.; Nardin, C. PD-L1 in circulating exosomes of Merkel cell carcinoma. *Exp. Dermatol.* **2022**, *31*, 869–877. [[CrossRef](#)] [[PubMed](#)]
185. Hu, L.; Chen, W.; Zhou, S.; Zhu, G. ExoHCR: A sensitive assay to profile PD-L1 level on tumor exosomes for immunotherapeutic prognosis. *Biophys. Rep.* **2020**, *6*, 290–298. [[CrossRef](#)]
186. Chen, X.; Du, Z.; Huang, M.; Wang, D.; Fong, W.P.; Liang, J.; Fan, L.; Wang, Y.; Yang, H.; Chen, Z.; et al. Circulating PD-L1 is associated with T cell infiltration and predicts prognosis in patients with CRLM following hepatic resection. *Cancer Immunol. Immunother.* **2022**, *71*, 661–674. [[CrossRef](#)] [[PubMed](#)]
187. Qiu, Y.; Yang, Y.; Yang, R.; Liu, C.; Hsu, J.M.; Jiang, Z.; Sun, L.; Wei, Y.; Li, C.W.; Yu, D.; et al. Activated T cell-derived exosomal PD-1 attenuates PD-L1-induced immune dysfunction in triple-negative breast cancer. *Oncogene* **2021**, *40*, 4992–5001. [[CrossRef](#)]
188. Wang, R.; Xu, A.; Zhang, X.; Wu, J.; Freywald, A.; Xu, J.; Xiang, J. Novel exosome-targeted T-cell-based vaccine counteracts T-cell energy and converts CTL exhaustion in chronic infection via CD40L signaling through the mTORC1 pathway. *Cell Mol. Immunol.* **2017**, *14*, 529–545. [[CrossRef](#)]
189. Morrissey, S.M.; Yan, J. Exosomal PD-L1: Roles in Tumor Progression and Immunotherapy. *Trends Cancer* **2020**, *6*, 550–558. [[CrossRef](#)]
190. Zhou, K.; Guo, S.; Li, F.; Sun, Q.; Liang, G. Exosomal PD-L1: New Insights into Tumor Immune Escape Mechanisms and Therapeutic Strategies. *Front. Cell Dev. Biol.* **2020**, *8*, 569219. [[CrossRef](#)]
191. Xie, F.; Xu, M.; Lu, J.; Mao, L.; Wang, S. The role of exosomal PD-L1 in tumor progression and immunotherapy. *Mol. Cancer* **2019**, *18*, 146. [[CrossRef](#)]
192. Liu, J.; Peng, X.; Yang, S.; Li, X.; Huang, M.; Wei, S.; Zhang, S.; He, G.; Zheng, H.; Fan, Q.; et al. Extracellular vesicle PD-L1 in reshaping tumor immune microenvironment: Biological function and potential therapy strategies. *Cell Commun. Signal.* **2022**, *20*, 14. [[CrossRef](#)] [[PubMed](#)]
193. Yoh, K.E.; Lowe, C.J.; Mahajan, S.; Suttman, R.; Nguy, T.; Reichelt, M.; Yang, J.; Melendez, R.; Li, Y.; Molinero, L.; et al. Enrichment of circulating tumor-derived extracellular vesicles from human plasma. *J. Immunol. Methods* **2021**, *490*, 112936. [[CrossRef](#)] [[PubMed](#)]
194. Wu, F.; Gu, Y.; Kang, B.; Heskia, F.; Pachot, A.; Bonneville, M.; Wei, P.; Liang, J. PD-L1 detection on circulating tumor-derived extracellular vesicles (T-EVs) from patients with lung cancer. *Transl. Lung Cancer Res.* **2021**, *10*, 2441–2451. [[CrossRef](#)] [[PubMed](#)]
195. Kim, D.H.; Kim, H.; Choi, Y.J.; Kim, S.Y.; Lee, J.E.; Sung, K.J.; Sung, Y.H.; Pack, C.G.; Jung, M.K.; Han, B.; et al. Exosomal PD-L1 promotes tumor growth through immune escape in non-small cell lung cancer. *Exp. Mol. Med.* **2019**, *51*, 1–13. [[CrossRef](#)]
196. Wang, Y.; Niu, X.; Cheng, Y.; Zhang, Y.; Xia, L.; Xia, W.; Lu, S. Exosomal PD-L1 predicts response with immunotherapy in NSCLC patients. *Clin. Exp. Immunol.* **2022**, *208*, 316–322. [[CrossRef](#)]
197. Shin, J.M.; Lee, C.H.; Son, S.; Kim, C.H.; Lee, J.A.; Ko, H.; Shin, S.; Song, S.H.; Park, S.S.; Bae, J.H.; et al. Sulfisoxazole Elicits Robust Antitumour Immune Response Along with Immune Checkpoint Therapy by Inhibiting Exosomal PD-L1. *Adv. Sci.* **2022**, *9*, e2103245. [[CrossRef](#)]
198. Gong, Y.; Li, K.; Qin, Y.; Zeng, K.; Liu, J.; Huang, S.; Chen, Y.; Yu, H.; Liu, W.; Ye, L.; et al. Norcholic Acid Promotes Tumor Progression and Immune Escape by Regulating Farnesoid X Receptor in Hepatocellular Carcinoma. *Front. Oncol.* **2021**, *11*, 711448. [[CrossRef](#)]
199. Shimada, Y.; Matsubayashi, J.; Kudo, Y.; Maehara, S.; Takeuchi, S.; Hagiwara, M.; Kakihana, M.; Ohira, T.; Nagao, T.; Ikeda, N. Serum-derived exosomal PD-L1 expression to predict anti-PD-1 response and in patients with non-small cell lung cancer. *Sci. Rep.* **2021**, *11*, 7830. [[CrossRef](#)]
200. Yin, Z.; Yu, M.; Ma, T.; Zhang, C.; Huang, S.; Karimzadeh, M.R.; Momtazi-Borojeni, A.A.; Chen, S. Mechanisms underlying low-clinical responses to PD-1/PD-L1 blocking antibodies in immunotherapy of cancer: A key role of exosomal PD-L1. *J. Immunother. Cancer* **2021**, *9*, e001698. [[CrossRef](#)]
201. Pico de Coaña, Y.; Wolodarski, M.; van der Haar Àvila, I.; Nakajima, T.; Rentouli, S.; Lundqvist, A.; Masucci, G.; Hansson, J.; Kiessling, R. PD-1 checkpoint blockade in advanced melanoma patients: NK cells, monocytic subsets and host PD-L1 expression as predictive biomarker candidates. *Oncoimmunology* **2020**, *9*, 1786888. [[CrossRef](#)]
202. Ando, K.; Hamada, K.; Shida, M.; Ohkuma, R.; Kubota, Y.; Horiike, A.; Matsui, H.; Ishiguro, T.; Hirasawa, Y.; Ariizumi, H.; et al. A high number of PD-L1⁺ CD14⁺ monocytes in peripheral blood is correlated with shorter survival in patients receiving immune checkpoint inhibitors. *Cancer Immunol. Immunother.* **2021**, *70*, 337–348. [[CrossRef](#)] [[PubMed](#)]
203. Lee, C.H.; Bae, J.H.; Choe, E.J.; Park, J.M.; Park, S.S.; Cho, H.J.; Song, B.J.; Baek, M.C. Macitentan improves antitumor immune responses by inhibiting the secretion of tumor-derived extracellular vesicle PD-L1. *Theranostics* **2022**, *12*, 1971–1987. [[CrossRef](#)] [[PubMed](#)]
204. Del Re, M.; van Schaik, R.H.N.; Fogli, S.; Mathijssen, R.H.J.; Cucchiara, F.; Capuano, A.; Scavone, C.; Jenster, G.W.; Danesi, R. Blood-based PD-L1 analysis in tumor-derived extracellular vesicles: Applications for optimal use of anti-PD-1/PD-L1 axis inhibitors. *Biochim. Biophys. Acta Rev. Cancer* **2021**, *1875*, 188463. [[CrossRef](#)] [[PubMed](#)]

205. Theodoraki, M.N.; Yerneni, S.S.; Hoffmann, T.K.; Gooding, W.E.; Whiteside, T.L. Clinical Significance of PD-L1⁺ Exosomes in Plasma of Head and Neck Cancer Patients. *Clin. Cancer Res.* **2018**, *24*, 896–905. [[CrossRef](#)] [[PubMed](#)]
206. Chen, H.L.; Luo, Y.P.; Lin, M.W.; Peng, X.X.; Liu, M.L.; Wang, Y.C.; Li, S.J.; Yang, D.H.; Yang, Z.X. Serum exosomal miR-16-5p functions as a tumor inhibitor and a new biomarker for PD-L1 inhibitor-dependent immunotherapy in lung adenocarcinoma by regulating PD-L1 expression. *Cancer Med.* **2022**, *11*, 2627–2643. [[CrossRef](#)]
207. Whiteside, T.L. The emerging role of plasma exosomes in diagnosis, prognosis and therapies of patients with cancer. *Contemp. Oncol.* **2018**, *22*, 38–40. [[CrossRef](#)]
208. Muller, L.; Muller-Haegeler, S.; Mitsushashi, M.; Gooding, W.; Okada, H.; Whiteside, T.L. Exosomes isolated from plasma of glioma patients enrolled in a vaccination trial reflect antitumor immune activity and might predict survival. *Oncoimmunology* **2015**, *4*, e1008347. [[CrossRef](#)]
209. Del Re, M.; Cucchiara, F.; Rofi, E.; Fontanelli, L.; Petrini, I.; Gri, N.; Pasquini, G.; Rizzo, M.; Gabelloni, M.; Belluomini, L.; et al. A multiparametric approach to improve the prediction of response to immunotherapy in patients with metastatic NSCLC. *Cancer Immunol. Immunother.* **2021**, *70*, 1667–1678. [[CrossRef](#)]
210. Tang, Y.; Zhang, P.; Wang, Y.; Wang, J.; Su, M.; Wang, Y.; Zhou, L.; Zhou, J.; Xiong, W.; Zeng, Z.; et al. The Biogenesis, Biology, and Clinical Significance of Exosomal PD-L1 in Cancer. *Front. Immunol.* **2020**, *11*, 604. [[CrossRef](#)]
211. Wang, M.; Zhai, X.; Li, J.; Guan, J.; Xu, S.; Li, Y.; Zhu, H. The Role of Cytokines in Predicting the Response and Adverse Events Related to Immune Checkpoint Inhibitors. *Front. Immunol.* **2021**, *12*, 670391. [[CrossRef](#)]
212. Cha, J.H.; Chan, L.C.; Li, C.W.; Hsu, J.L.; Hung, M.C. Mechanisms Controlling PD-L1 Expression in Cancer. *Mol. Cell* **2019**, *76*, 359–370. [[CrossRef](#)] [[PubMed](#)]
213. Yi, M.; Niu, M.; Xu, L.; Luo, S.; Wu, K. Regulation of PD-L1 expression in the tumor microenvironment. *J. Hematol. Oncol.* **2021**, *14*, 10. [[CrossRef](#)] [[PubMed](#)]
214. Fan, Y.; Che, X.; Qu, J.; Hou, K.; Wen, T.; Li, Z.; Li, C.; Wang, S.; Xu, L.; Liu, Y.; et al. Exosomal PD-L1 Retains Immunosuppressive Activity and is Associated with Gastric Cancer Prognosis. *Ann. Surg. Oncol.* **2019**, *26*, 3745–3755. [[CrossRef](#)] [[PubMed](#)]
215. Liu, C.; Wang, Y.; Li, L.; He, D.; Chi, J.; Li, Q.; Wu, Y.; Zhao, Y.; Zhang, S.; Wang, L.; et al. Engineered extracellular vesicles and their mimetics for cancer immunotherapy. *J. Control. Release* **2022**, *349*, 679–698. [[CrossRef](#)]
216. Yong, T.; Wei, Z.; Gan, L.; Yang, X. Extracellular Vesicle-Based Drug Delivery Systems for Enhanced Anti-Tumor Therapies through Modulating Cancer-Immunity Cycle. *Adv. Mater.* **2022**, *20*, e2201054. [[CrossRef](#)]
217. Ding, Y.; Wang, L.; Li, H.; Miao, F.; Zhang, Z.; Hu, C.; Yu, W.; Tang, Q.; Shao, G. Application of lipid nanovesicle drug delivery system in cancer immunotherapy. *J. Nanobiotechnol.* **2022**, *20*, 214. [[CrossRef](#)]
218. Calvo, V.; Izquierdo, M. T Lymphocyte and CAR-T Cell-Derived Extracellular Vesicles and Their Applications in Cancer Therapy. *Cells* **2022**, *11*, 790. [[CrossRef](#)]
219. Hao, Q.; Wu, Y.; Wu, Y.; Wang, P.; Vadgama, J.V. Tumor-Derived Exosomes in Tumor-Induced Immune Suppression. *Int. J. Mol. Sci.* **2022**, *23*, 1461. [[CrossRef](#)]
220. Hosseini, R.; Sarvnaz, H.; Arabpour, M.; Ramshe, S.M.; Asef-Kabiri, L.; Yousefi, H.; Akbari, M.E.; Eskandari, N. Cancer exosomes and natural killer cells dysfunction: Biological roles, clinical significance and implications for immunotherapy. *Mol. Cancer* **2022**, *21*, 15. [[CrossRef](#)]
221. Abu, N.; Rus Bakaruraini, N.A.A. The interweaving relationship between extracellular vesicles and T cells in cancer. *Cancer Lett.* **2022**, *530*, 1–7. [[CrossRef](#)]
222. Shenoy, G.N.; Bhatta, M.; Bankert, R.B. Tumor-Associated Exosomes: A Potential Therapeutic Target for Restoring Anti-Tumor T Cell Responses in Human Tumor Microenvironments. *Cells* **2021**, *10*, 3155. [[CrossRef](#)] [[PubMed](#)]
223. Ma, F.; Vayalil, J.; Lee, G.; Wang, Y.; Peng, G. Emerging role of tumor-derived extracellular vesicles in T cell suppression and dysfunction in the tumor microenvironment. *J. Immunother. Cancer* **2021**, *9*, e003217. [[CrossRef](#)] [[PubMed](#)]
224. Wang, M.; Zhang, B. The Immunomodulation Potential of Exosomes in Tumor Microenvironment. *J. Immunol. Res.* **2021**, *2021*, 3710372. [[CrossRef](#)] [[PubMed](#)]
225. Linder, M.; Pogge von Strandmann, E. The Role of Extracellular HSP70 in the Function of Tumor-Associated Immune Cells. *Cancers* **2021**, *13*, 4721. [[CrossRef](#)] [[PubMed](#)]
226. Li, Q.; Cai, S.; Li, M.; Salma, K.I.; Zhou, X.; Han, F.; Chen, J.; Huyan, T. Tumor-Derived Extracellular Vesicles: Their Role in Immune Cells and Immunotherapy. *Int. J. Nanomed.* **2021**, *16*, 5395–5409. [[CrossRef](#)]
227. Wu, F.; Xie, M.; Hun, M.; She, Z.; Li, C.; Luo, S.; Chen, X.; Wan, W.; Wen, C.; Tian, J. Natural Killer Cell-Derived Extracellular Vesicles: Novel Players in Cancer Immunotherapy. *Front. Immunol.* **2021**, *12*, 658698. [[CrossRef](#)]
228. Hou, P.P.; Chen, H.Z. Extracellular vesicles in the tumor immune microenvironment. *Cancer Lett.* **2021**, *516*, 48–56. [[CrossRef](#)]
229. Lipinski, S.; Tiemann, K. Extracellular Vesicles and Their Role in the Spatial and Temporal Expansion of Tumor-Immune Interactions. *Int. J. Mol. Sci.* **2021**, *22*, 3374. [[CrossRef](#)]
230. Ayala-Mar, S.; Donoso-Quezada, J.; González-Valdez, J. Clinical Implications of Exosomal PD-L1 in Cancer Immunotherapy. *J. Immunol. Res.* **2021**, *2021*, 8839978. [[CrossRef](#)]
231. Wang, L.; Sun, Z.; Wang, H. Extracellular vesicles and the regulation of tumor immunity: Current progress and future directions. *J. Cell Biochem.* **2021**, *122*, 760–769. [[CrossRef](#)]
232. Srivastava, A.; Rathore, S.; Munshi, A.; Ramesh, R. Extracellular Vesicles in Oncology: From Immune Suppression to Immunotherapy. *AAPS J.* **2021**, *23*, 30. [[CrossRef](#)] [[PubMed](#)]

233. Lucafò, M.; De Biasi, S.; Curci, D.; Norbedo, A.; Stocco, G.; Decorti, G. Extracellular Vesicles as Innovative Tools for Assessing Adverse Effects of Immunosuppressant Drugs. *Curr. Med. Chem.* **2022**, *29*, 3586–3600. [[CrossRef](#)] [[PubMed](#)]
234. Negahdaripour, M.; Owji, H.; Eskandari, S.; Zamani, M.; Vakili, B.; Nezafat, N. Small extracellular vesicles (sEVs): Discovery, functions, applications, detection methods and various engineered forms. *Expert Opin. Biol. Ther.* **2021**, *21*, 371–394. [[CrossRef](#)] [[PubMed](#)]
235. Jiang, X.C.; Zhang, T.; Gao, J.Q. The in vivo fate and targeting engineering of crossover vesicle-based gene delivery system. *Adv. Drug Deliv. Rev.* **2022**, *187*, 114324. [[CrossRef](#)]
236. Raghav, A.; Jeong, G.B. A systematic review on the modifications of extracellular vesicles: A revolutionized tool of nanobiotechnology. *J. Nanobiotechnol.* **2021**, *19*, 459. [[CrossRef](#)]
237. Kućuk, N.; Primožič, M.; Knez, Ž.; Leitgeb, M. Exosomes Engineering and Their Roles as Therapy Delivery Tools, Therapeutic Targets, and Biomarkers. *Int. J. Mol. Sci.* **2021**, *22*, 9543. [[CrossRef](#)]
238. Liang, Y.; Duan, L.; Lu, J.; Xia, J. Engineering exosomes for targeted drug delivery. *Theranostics* **2021**, *11*, 3183–3195. [[CrossRef](#)]
239. Geng, T.; Pan, P.; Leung, E.; Chen, Q.; Chamley, L.; Wu, Z. Recent Advancement and Technical Challenges in Developing Small Extracellular Vesicles for Cancer Drug Delivery. *Pharm. Res.* **2021**, *38*, 179–197. [[CrossRef](#)]
240. Xue, V.W.; Wong, S.C.C.; Song, G.; Cho, W.C.S. Promising RNA-based cancer gene therapy using extracellular vesicles for drug delivery. *Expert Opin. Biol. Ther.* **2020**, *20*, 767–777. [[CrossRef](#)]
241. Jablkowski, M.; Szemraj, M.; Oszajca, K.; Janiszewska, G.; Bartkowiak, J.; Szemraj, J. New type of BACE1 siRNA delivery to cells. *Med. Sci. Monit.* **2014**, *20*, 2598–2606. [[CrossRef](#)]
242. Nawrot, B. Targeting BACE with small inhibitory nucleic acids—A future for Alzheimer’s disease therapy? *Acta Biochim. Pol.* **2004**, *51*, 431–444. [[CrossRef](#)]
243. Alvarez-Erviti, L.; Seow, Y.; Yin, H.; Betts, C.; Lakhali, S.; Wood, M.J. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat. Biotechnol.* **2011**, *29*, 341–345. [[CrossRef](#)] [[PubMed](#)]
244. Meldolesi, J. News about Therapies of Alzheimer’s Disease: Extracellular Vesicles from Stem Cells Exhibit Advantages Compared to Other Treatments. *Biomedicines* **2022**, *10*, 105. [[CrossRef](#)] [[PubMed](#)]
245. Zhang, Y.; Liu, Q.; Zhang, X.; Huang, H.; Tang, S.; Chai, Y.; Xu, Z.; Li, M.; Chen, X.; Liu, J.; et al. Recent advances in exosome-mediated nucleic acid delivery for cancer therapy. *J. Nanobiotechnol.* **2022**, *20*, 279. [[CrossRef](#)] [[PubMed](#)]
246. Entezari, M.; Ghanbarirad, M.; Taheriazam, A.; Sadrkhanloo, M.; Zabolian, A.; Goharrizi, M.A.S.B.; Hushmandi, K.; Aref, A.R.; Ashrafizadeh, M.; Zarrabi, A.; et al. Long non-coding RNAs and exosomal lncRNAs: Potential functions in lung cancer progression, drug resistance and tumor microenvironment remodeling. *Biomed. Pharmacother.* **2022**, *150*, 112963. [[CrossRef](#)] [[PubMed](#)]
247. Taghvimi, S.; Vakili, O.; Soltani Fard, E.; Khatami, S.H.; Karami, N.; Taheri-Anganeh, M.; Salehi, M.; Negahdari, B.; Ghasemi, H.; Movahedpour, A. Exosomal microRNAs and long noncoding RNAs: Novel mediators of drug resistance in lung cancer. *J. Cell Physiol.* **2022**, *237*, 2095–2106. [[CrossRef](#)]
248. Sohrabi, B.; Dayeri, B.; Zahedi, E.; Khoshbakht, S.; Nezamabadi Pour, N.; Ranjbar, H.; Davari Nejad, A.; Nouredini, M.; Alani, B. Mesenchymal stem cell (MSC)-derived exosomes as novel vehicles for delivery of miRNAs in cancer therapy. *Cancer Gene Ther.* **2022**, *29*, 1105–1116. [[CrossRef](#)]
249. Sorop, A.; Constantinescu, D.; Cojocaru, F.; Dinischiotu, A.; Cucu, D.; Dima, S.O. Exosomal microRNAs as Biomarkers and Therapeutic Targets for Hepatocellular Carcinoma. *Int. J. Mol. Sci.* **2021**, *22*, 4997. [[CrossRef](#)]
250. Mohammadi, R.; Hosseini, S.A.; Noruzi, S.; Ebrahimzadeh, A.; Sahebkar, A. Diagnostic and Therapeutic Applications of Exosome Nanovesicles in Lung Cancer: State-of-The-Art. *Anticancer Agents Med. Chem.* **2022**, *22*, 83–100. [[CrossRef](#)]
251. Li, X.; Jiang, W.; Gan, Y.; Zhou, W. The Application of Exosomal MicroRNAs in the Treatment of Pancreatic Cancer and Its Research Progress. *Pancreas* **2021**, *50*, 12–16. [[CrossRef](#)]
252. Mowla, M.; Hashemi, A. Functional roles of exosomal miRNAs in multi-drug resistance in cancer chemotherapeutics. *Exp. Mol. Pathol.* **2021**, *118*, 104592. [[CrossRef](#)] [[PubMed](#)]
253. Nakase, I.; Kobayashi, N.B.; Takatani-Nakase, T.; Yoshida, T. Active macropinocytosis induction by stimulation of epidermal growth factor receptor and oncogenic Ras expression potentiates cellular uptake efficacy of exosomes. *Sci. Rep.* **2015**, *5*, 10300. [[CrossRef](#)] [[PubMed](#)]
254. Nakagawa, Y.; Arafiles, J.V.V.; Kawaguchi, Y.; Nakase, I.; Hirose, H.; Futaki, S. Stearylated Macropinocytosis-Inducing Peptides Facilitating the Cellular Uptake of Small Extracellular Vesicles. *Bioconjug. Chem.* **2022**, *33*, 869–880. [[CrossRef](#)]
255. Noguchi, K.; Obuki, M.; Sumi, H.; Klusmann, M.; Morimoto, K.; Nakai, S.; Hashimoto, T.; Fujiwara, D.; Fujii, I.; Yuba, E.; et al. Macropinocytosis-Inducible Extracellular Vesicles Modified with Antimicrobial Protein CAP18-Derived Cell-Penetrating Peptides for Efficient Intracellular Delivery. *Mol. Pharm.* **2021**, *18*, 3290–3301. [[CrossRef](#)]
256. Takenaka, T.; Nakai, S.; Katayama, M.; Hirano, M.; Ueno, N.; Noguchi, K.; Takatani-Nakase, T.; Fujii, I.; Kobayashi, S.S.; Nakase, I. Effects of gefitinib treatment on cellular uptake of extracellular vesicles in EGFR-mutant non-small cell lung cancer cells. *Int. J. Pharm.* **2019**, *572*, 118762. [[CrossRef](#)]
257. Nakase, I.; Noguchi, K.; Aoki, A.; Takatani-Nakase, T.; Fujii, I.; Futaki, S. Arginine-rich cell-penetrating peptide-modified extracellular vesicles for active macropinocytosis induction and efficient intracellular delivery. *Sci. Rep.* **2017**, *7*, 1991. [[CrossRef](#)] [[PubMed](#)]

258. Nakase, I.; Noguchi, K.; Fujii, I.; Futaki, S. Vectorization of biomacromolecules into cells using extracellular vesicles with enhanced internalization induced by macropinocytosis. *Sci. Rep.* **2016**, *6*, 34937. [\[CrossRef\]](#)
259. Nakase, I.; Takatani-Nakase, T. Exosomes: Breast cancer-derived extracellular vesicles; recent key findings and technologies in disease progression, diagnostics, and cancer targeting. *Drug Metab. Pharmacokinet.* **2022**, *42*, 100435. [\[CrossRef\]](#)
260. Noguchi, K.; Hirano, M.; Hashimoto, T.; Yuba, E.; Takatani-Nakase, T.; Nakase, I. Effects of Lyophilization of Arginine-rich Cell-penetrating Peptide-modified Extracellular Vesicles on Intracellular Delivery. *Anticancer Res.* **2019**, *39*, 6701–6709. [\[CrossRef\]](#)
261. Siddiqui, H.; Yevstigneyev, N.; Madani, G.; McCormick, S. Approaches to Visualising Endocytosis of LDL-Related Lipoproteins. *Biomolecules* **2022**, *12*, 158. [\[CrossRef\]](#)
262. Varma, S.; Dey, S.; Palanisamy, D. Cellular Uptake Pathways of Nanoparticles: Process of Endocytosis and Factors Affecting their Fate. *Curr. Pharm. Biotechnol.* **2022**, *23*, 679–706. [\[CrossRef\]](#)
263. Cooke, L.D.F.; Tumbarello, D.A.; Harvey, N.C.; Sethi, J.K.; Lewis, R.M.; Cleal, J.K. Endocytosis in the placenta: An undervalued mediator of placental transfer. *Placenta* **2021**, *113*, 67–73. [\[CrossRef\]](#) [\[PubMed\]](#)
264. Vieira, N.; Rito, T.; Correia-Neves, M.; Sousa, N. Sorting Out Sorting Nexins Functions in the Nervous System in Health and Disease. *Mol. Neurobiol.* **2021**, *58*, 4070–4106. [\[CrossRef\]](#) [\[PubMed\]](#)
265. Renard, H.F.; Boucrot, E. Unconventional endocytic mechanisms. *Curr. Opin. Cell Biol.* **2021**, *71*, 120–129. [\[CrossRef\]](#) [\[PubMed\]](#)
266. Mushtaq, A.; Li, L.A.A.; Grøndahl, L. Chitosan Nanomedicine in Cancer Therapy: Targeted Delivery and Cellular Uptake. *Macromol. Biosci.* **2021**, *21*, e2100005. [\[CrossRef\]](#) [\[PubMed\]](#)
267. Kahlhofer, J.; Leon, S.; Teis, D.; Schmidt, O. The α -arrestin family of ubiquitin ligase adaptors links metabolism with selective endocytosis. *Biol. Cell* **2021**, *113*, 183–219. [\[CrossRef\]](#) [\[PubMed\]](#)
268. Luk, B.T.; Zhang, L. Cell membrane-camouflaged nanoparticles for drug delivery. *J. Control. Release* **2015**, *220*, 600–607. [\[CrossRef\]](#)
269. Lee, N.H.; You, S.; Taghizadeh, A.; Taghizadeh, M.; Kim, H.S. Cell Membrane-Cloaked Nanotherapeutics for Targeted Drug Delivery. *Int. J. Mol. Sci.* **2022**, *23*, 2223. [\[CrossRef\]](#)
270. Smith, S.M.; Smith, C.J. Capturing the mechanics of clathrin-mediated endocytosis. *Curr. Opin. Struct. Biol.* **2022**, *75*, 102427. [\[CrossRef\]](#)
271. Shi, R.; Hou, L.; Wei, L.; Liu, J. Involvement of adaptor proteins in clathrin-mediated endocytosis of virus entry. *Microb. Pathog.* **2021**, *161*, 105278. [\[CrossRef\]](#)
272. Redlingshöfer, L.; Brodsky, F.M. Antagonistic regulation controls clathrin-mediated endocytosis: AP2 adaptor facilitation vs restraint from clathrin light chains. *Cells Dev.* **2021**, *168*, 203714. [\[CrossRef\]](#) [\[PubMed\]](#)
273. Moo, E.V.; van Senten, J.R.; Bräuner-Osborne, H.; Møller, T.C. Arrestin-Dependent and -Independent Internalization of G Protein-Coupled Receptors: Methods, Mechanisms, and Implications on Cell Signaling. *Mol. Pharmacol.* **2021**, *99*, 242–255. [\[CrossRef\]](#) [\[PubMed\]](#)
274. Li, W.; Hu, J.; Li, X.; Lu, Z.; Li, X.; Wang, C.; Yu, S. Receptor-Dependent Endocytosis Mediates α -Synuclein Oligomer Transport into Red Blood Cells. *Front. Aging Neurosci.* **2022**, *14*, 899892. [\[CrossRef\]](#) [\[PubMed\]](#)
275. Singh, M.; Jadhav, H.R.; Bhatt, T. Dynamin Functions and Ligands: Classical Mechanisms Behind. *Mol. Pharmacol.* **2017**, *91*, 123–134. [\[CrossRef\]](#)
276. Wolfe, B.L.; Trejo, J. Clathrin-dependent mechanisms of G protein-coupled receptor endocytosis. *Traffic* **2007**, *8*, 462–470. [\[CrossRef\]](#)
277. Rejman, J.; Oberle, V.; Zuhorn, I.S.; Hoekstra, D. Size-dependent internalization of particles via the pathways of clathrin- and caveolae-mediated endocytosis. *Biochem. J.* **2004**, *377*, 159–169. [\[CrossRef\]](#)
278. Langston Suen, W.L.; Chau, Y. Size-dependent internalisation of folate-decorated nanoparticles via the pathways of clathrin and caveolae-mediated endocytosis in ARPE-19 cells. *J. Pharm. Pharmacol.* **2014**, *66*, 564–573. [\[CrossRef\]](#)
279. Hackett, B.A.; Cherry, S. Flavivirus internalization is regulated by a size-dependent endocytic pathway. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 4246–4251. [\[CrossRef\]](#)
280. Ueda, Y.; Sato, M. Cell membrane dynamics induction using optogenetic tools. *Biochem. Biophys. Res. Commun.* **2018**, *506*, 387–393. [\[CrossRef\]](#)
281. Gozzelino, L.; De Santis, M.C.; Gulluni, F.; Hirsch, E.; Martini, M. PI(3, 4)P2 Signaling in Cancer and Metabolism. *Front. Oncol.* **2020**, *10*, 360. [\[CrossRef\]](#)
282. Liu, H.; Qian, F. Exploiting macropinocytosis for drug delivery into KRAS mutant cancer. *Theranostics* **2022**, *12*, 1321–1332. [\[CrossRef\]](#) [\[PubMed\]](#)
283. Liu, X.; Ghosh, D. Intracellular nanoparticle delivery by oncogenic KRAS-mediated macropinocytosis. *Int. J. Nanomed.* **2019**, *14*, 6589–6600. [\[CrossRef\]](#) [\[PubMed\]](#)
284. Michalopoulou, E.; Auciello, F.R.; Bulusu, V.; Strachan, D.; Campbell, A.D.; Tait-Mulder, J.; Karim, S.A.; Morton, J.P.; Sansom, O.J.; Kamphorst, J.J. Macropinocytosis Renders a Subset of Pancreatic Tumor Cells Resistant to mTOR Inhibition. *Cell Rep.* **2020**, *30*, 2729–2742.e4. [\[CrossRef\]](#) [\[PubMed\]](#)
285. Zhang, M.S.; Cui, J.D.; Lee, D.; Yuen, V.W.; Chiu, D.K.; Goh, C.C.; Cheu, J.W.; Tse, A.P.; Bao, M.H.; Wong, B.P.Y.; et al. Hypoxia-induced macropinocytosis represents a metabolic route for liver cancer. *Nat. Commun.* **2022**, *13*, 954. [\[CrossRef\]](#)
286. Recouvreux, M.V.; Commisso, C. Macropinocytosis: A Metabolic Adaptation to Nutrient Stress in Cancer. *Front. Endocrinol.* **2017**, *8*, 261. [\[CrossRef\]](#) [\[PubMed\]](#)
287. Commisso, C. The pervasiveness of macropinocytosis in oncological malignancies. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2019**, *374*, 20180153. [\[CrossRef\]](#)

288. Sutton, M.N.; Gammon, S.T.; Muzzioli, R.; Pisaneschi, F.; Radaram, B.; Yang, P.; Piwnica-Worms, D. RAS-Driven Macropinocytosis of Albumin or Dextran Reveals Mutation-Specific Target Engagement of RAS p.G12C Inhibitor ARS-1620 by NIR-Fluorescence Imaging. *Mol. Imaging Biol.* **2022**, *24*, 498–509. [[CrossRef](#)]
289. Sheng, W.; Geng, J.; Li, L.; Shang, Y.; Jiang, M.; Zhen, Y. An albumin-binding domain and targeting peptide-based recombinant protein and its enediyne-integrated analogue exhibit directional delivery and potent inhibitory activity on pancreatic cancer with K-ras mutation. *Oncol. Rep.* **2020**, *43*, 851–863. [[CrossRef](#)]
290. Thu, P.M.; Zheng, Z.G.; Zhou, Y.P.; Wang, Y.Y.; Zhang, X.; Jing, D.; Cheng, H.M.; Li, J.; Li, P.; Xu, X. Phellodendrine chloride suppresses proliferation of KRAS mutated pancreatic cancer cells through inhibition of nutrients uptake via macropinocytosis. *Eur. J. Pharmacol.* **2019**, *850*, 23–34. [[CrossRef](#)]
291. Zhang, Y.; Wei, Y.; Liu, P.; Zhang, X.; Xu, Z.; Tan, X.; Chen, M.; Wang, J. ICP-MS and Photothermal Dual-Readout Assay for Ultrasensitive and Point-of-Care Detection of Pancreatic Cancer Exosomes. *Anal. Chem.* **2021**, *93*, 11540–11546. [[CrossRef](#)]
292. Buscail, E.; Alix-Panabières, C.; Quincy, P.; Cauvin, T.; Chauvet, A.; Degrandi, O.; Caumont, C.; Verdon, S.; Lamrissi, I.; Moranvillier, I.; et al. High Clinical Value of Liquid Biopsy to Detect Circulating Tumor Cells and Tumor Exosomes in Pancreatic Ductal Adenocarcinoma Patients Eligible for Up-Front Surgery. *Cancers* **2019**, *11*, 1656. [[CrossRef](#)] [[PubMed](#)]
293. Xiao, D.; Dong, Z.; Zhen, L.; Xia, G.; Huang, X.; Wang, T.; Guo, H.; Yang, B.; Xu, C.; Wu, W.; et al. Combined Exosomal GPC1, CD82, and Serum CA19-9 as Multiplex Targets: A Specific, Sensitive, and Reproducible Detection Panel for the Diagnosis of Pancreatic Cancer. *Mol. Cancer Res.* **2020**, *18*, 300–310. [[CrossRef](#)] [[PubMed](#)]
294. Buscail, E.; Chauvet, A.; Quincy, P.; Degrandi, O.; Buscail, C.; Lamrissi, I.; Moranvillier, I.; Caumont, C.; Verdon, S.; Brisson, A.; et al. CD63-GPC1-Positive Exosomes Coupled with CA19-9 Offer Good Diagnostic Potential for Resectable Pancreatic Ductal Adenocarcinoma. *Transl. Oncol.* **2019**, *12*, 1395–1403. [[CrossRef](#)] [[PubMed](#)]
295. Zanetti-Domingues, L.C.; Bonner, S.E.; Iyer, R.S.; Martin-Fernandez, M.L.; Huber, V. Cooperation and Interplay between EGFR Signalling and Extracellular Vesicle Biogenesis in Cancer. *Cells* **2020**, *9*, 2639. [[CrossRef](#)] [[PubMed](#)]
296. Gonda, A.; Kabagwira, J.; Senthil, G.N.; Wall, N.R. Internalization of Exosomes through Receptor-Mediated Endocytosis. *Mol. Cancer Res.* **2019**, *17*, 337–347. [[CrossRef](#)]
297. Ramos-Zaldívar, H.M.; Polakovícova, I.; Salas-Huenuleo, E.; Corvalán, A.H.; Kogan, M.J.; Yefi, C.P.; Andia, M.E. Extracellular vesicles through the blood-brain barrier: A review. *Fluids Barriers CNS* **2022**, *19*, 60. [[CrossRef](#)]
298. Nakase, I. Biofunctional Peptide-Modified Extracellular Vesicles Enable Effective Intracellular Delivery via the Induction of Macropinocytosis. *Processes* **2021**, *9*, 224. [[CrossRef](#)]
299. Sun, W.; Ren, Y.; Lu, Z.; Zhao, X. The potential roles of exosomes in pancreatic cancer initiation and metastasis. *Mol. Cancer* **2020**, *19*, 135. [[CrossRef](#)]
300. Beit-Yannai, E.; Tabak, S.; Stamer, W.D. Physical exosome:exosome interactions. *J. Cell Mol. Med.* **2018**, *22*, 2001–2006. [[CrossRef](#)]
301. Midekessa, G.; Godakumara, K.; Ord, J.; Viil, J.; Lättেকivi, F.; Dissanayake, K.; Kopanchuk, S.; Rinken, A.; Andronowska, A.; Bhattacharjee, S.; et al. Zeta Potential of Extracellular Vesicles: Toward Understanding the Attributes that Determine Colloidal Stability. *ACS Omega* **2020**, *5*, 16701–16710. [[CrossRef](#)]
302. Kesimer, M.; Gupta, R. Physical characterization and profiling of airway epithelial derived exosomes using light scattering. *Methods* **2015**, *87*, 59–63. [[CrossRef](#)]
303. Yang, Y.; Shen, G.; Wang, H.; Li, H.; Zhang, T.; Tao, N.; Ding, X.; Yu, H. Interferometric plasmonic imaging and detection of single exosomes. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 10275–10280. [[CrossRef](#)] [[PubMed](#)]
304. Pedrioli, G.; Paganetti, P. Hijacking Endocytosis and Autophagy in Extracellular Vesicle Communication: Where the Inside Meets the Outside. *Front. Cell Dev. Biol.* **2021**, *8*, 595515. [[CrossRef](#)] [[PubMed](#)]
305. Kamerkar, S.; LeBleu, V.S.; Sugimoto, H.; Yang, S.; Ruivo, C.F.; Melo, S.A.; Lee, J.J.; Kalluri, R. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature* **2017**, *546*, 498–503. [[CrossRef](#)] [[PubMed](#)]
306. Yuan, F.; Sun, M.; Liu, Z.; Liu, H.; Kong, W.; Wang, R.; Qian, F. Macropinocytic dextran facilitates KRAS-targeted delivery while reducing drug-induced tumor immunity depletion in pancreatic cancer. *Theranostics* **2022**, *12*, 1061–1073. [[CrossRef](#)]
307. Mendt, M.; Kamerkar, S.; Sugimoto, H.; McAndrews, K.M.; Wu, C.C.; Gagea, M.; Yang, S.; Blanco, E.V.R.; Peng, Q.; Ma, X.; et al. Generation and testing of clinical-grade exosomes for pancreatic cancer. *JCI Insight* **2018**, *3*, e99263. [[CrossRef](#)]
308. Zhao, Z.; Zhao, G.; Yang, S.; Zhu, S.; Zhang, S.; Li, P. The significance of exosomal RNAs in the development, diagnosis, and treatment of pancreatic cancer. *Cancer Cell Int.* **2021**, *21*, 364. [[CrossRef](#)]
309. Jing, C.; Cao, H.; Qin, X.; Yu, S.; Wu, J.; Wang, Z.; Ma, R.; Feng, J. Exosome-mediated gefitinib resistance in lung cancer HCC827 cells via delivery of miR-21. *Oncol. Lett.* **2018**, *15*, 9811–9817. [[CrossRef](#)]
310. Srivastava, A.; Amreddy, N.; Babu, A.; Panneerselvam, J.; Mehta, M.; Muralidharan, R.; Chen, A.; Zhao, Y.D.; Razaq, M.; Riedinger, N.; et al. Nanosomes carrying doxorubicin exhibit potent anticancer activity against human lung cancer cells. *Sci. Rep.* **2016**, *6*, 38541. [[CrossRef](#)]
311. Rizwan, M.N.; Ma, Y.; Nenkov, M.; Jin, L.; Schröder, D.C.; Westermann, M.; Gaßler, N.; Chen, Y. Tumor-derived exosomes: Key players in non-small cell lung cancer metastasis and their implication for targeted therapy. *Mol. Carcinog.* **2022**, *61*, 269–280. [[CrossRef](#)]
312. Nakase, I. Development of Intracellular Delivery System Based on Biofunctional Peptide-modified Exosome. *Membrane* **2016**, *41*, 209–214. [[CrossRef](#)]

313. Sancho-Albero, M.; Sebastián, V.; Sesé, J.; Pazo-Cid, R.; Mendoza, G.; Arruebo, M.; Martín-Duque, P.; Santamaría, J. Isolation of exosomes from whole blood by a new microfluidic device: Proof of concept application in the diagnosis and monitoring of pancreatic cancer. *J. Nanobiotechnol.* **2020**, *18*, 150. [[CrossRef](#)] [[PubMed](#)]
314. Nakase, I.; Akita, H.; Kogure, K.; Gräslund, A.; Langel, U.; Harashima, H.; Futaki, S. Efficient intracellular delivery of nucleic acid pharmaceuticals using cell-penetrating peptides. *Acc. Chem. Res.* **2012**, *45*, 1132–1139. [[CrossRef](#)]
315. Nakase, I.; Ueno, N.; Katayama, M.; Noguchi, K.; Takatani-Nakase, T.; Kobayashi, N.B.; Yoshida, T.; Fujii, I.; Futaki, S. Receptor clustering and activation by multivalent interaction through recognition peptides presented on exosomes. *Chem. Commun.* **2016**, *53*, 317–320. [[CrossRef](#)] [[PubMed](#)]
316. Futaki, S.; Nakase, I. Cell-Surface Interactions on Arginine-Rich Cell-Penetrating Peptides Allow for Multiplex Modes of Internalization. *Acc. Chem. Res.* **2017**, *50*, 2449–2456. [[CrossRef](#)]
317. Nakase, I.; Osaki, K.; Tanaka, G.; Utani, A.; Futaki, S. Molecular interplays involved in the cellular uptake of octaarginine on cell surfaces and the importance of syndecan-4 cytoplasmic V domain for the activation of protein kinase C α . *Biochem. Biophys. Res. Commun.* **2014**, *446*, 857–862. [[CrossRef](#)]
318. Albrecht, L.V.; Tejada-Muñoz, N.; Bui, M.H.; Cicchetto, A.C.; Di Biagio, D.; Colozza, G.; Schmid, E.; Piccolo, S.; Christofk, H.R.; De Robertis, E.M. GSK3 Inhibits Macropinocytosis and Lysosomal Activity through the Wnt Destruction Complex Machinery. *Cell Rep.* **2020**, *32*, 107973. [[CrossRef](#)]
319. Reggiori, F.; Gabius, H.J.; Aureli, M.; Römer, W.; Sonnino, S.; Eskelinen, E.L. Glycans in autophagy, endocytosis and lysosomal functions. *Glycoconj. J.* **2021**, *38*, 625–647. [[CrossRef](#)]
320. Kobayashi, S.; Nakase, I.; Kawabata, N.; Yu, H.H.; Pujals, S.; Imanishi, M.; Giralt, E.; Futaki, S. Cytosolic targeting of macromolecules using a pH-dependent fusogenic peptide in combination with cationic liposomes. *Bioconjug. Chem.* **2009**, *20*, 953–959. [[CrossRef](#)]
321. Nakase, I.; Kogure, K.; Harashima, H.; Futaki, S. Application of a fusogenic peptide GALA for intracellular delivery. *Methods Mol. Biol.* **2011**, *683*, 525–533. [[CrossRef](#)]
322. Nakase, I.; Futaki, S. Combined treatment with a pH-sensitive fusogenic peptide and cationic lipids achieves enhanced cytosolic delivery of exosomes. *Sci. Rep.* **2015**, *5*, 10112. [[CrossRef](#)] [[PubMed](#)]
323. Matsuzaka, Y.; Tanihata, J.; Komaki, H.; Ishiyama, A.; Oya, Y.; Rüegg, U.; Takeda, S.I.; Hashido, K. Characterization and Functional Analysis of Extracellular Vesicles and Muscle-Abundant miRNAs (miR-1, miR-133a, and miR-206) in C2C12 Myocytes and mdx Mice. *PLoS ONE* **2016**, *11*, e0167811. [[CrossRef](#)] [[PubMed](#)]
324. Sivanantham, A.; Jin, Y. Impact of Storage Conditions on EV Integrity/Surface Markers and Cargos. *Life* **2022**, *12*, 697. [[CrossRef](#)] [[PubMed](#)]
325. Wu, J.Y.; Li, Y.J.; Hu, X.B.; Huang, S.; Xiang, D.X. Preservation of small extracellular vesicles for functional analysis and therapeutic applications: A comparative evaluation of storage conditions. *Drug Deliv.* **2021**, *28*, 162–170. [[CrossRef](#)] [[PubMed](#)]
326. Zhang, Y.; Bi, J.; Huang, J.; Tang, Y.; Du, S.; Li, P. Exosome: A Review of Its Classification, Isolation Techniques, Storage, Diagnostic and Targeted Therapy Applications. *Int. J. Nanomed.* **2020**, *15*, 6917–6934. [[CrossRef](#)] [[PubMed](#)]
327. Jayaram, A.; Jay, S.M. Preservation and Storage Stability of Extracellular Vesicles for Therapeutic Applications. *AAPS J.* **2017**, *20*, 1. [[CrossRef](#)]
328. Görgens, A.; Corso, G.; Hagey, D.W.; Jawad Wiklander, R.; Gustafsson, M.O.; Felldin, U.; Lee, Y.; Bostancioglu, R.B.; Sork, H.; Liang, X.; et al. Identification of storage conditions stabilizing extracellular vesicles preparations. *J. Extracell. Vesicles* **2022**, *11*, e12238. [[CrossRef](#)]
329. Deville, S.; Berckmans, P.; Van Hoof, R.; Lambrichts, I.; Salvati, A.; Nelissen, I. Comparison of extracellular vesicle isolation and storage methods using high-sensitivity flow cytometry. *PLoS ONE* **2021**, *16*, e0245835. [[CrossRef](#)]
330. Tsuchiya, A.; Terai, S.; Horiguchi, I.; Homma, Y.; Saito, A.; Nakamura, N.; Sato, Y.; Ochiya, T.; Kino-Oka, M.; Working Group of Attitudes for Preparation and Treatment of Exosomes of Japanese Society of Regenerative Medicine. Basic points to consider regarding the preparation of extracellular vesicles and their clinical applications in Japan. *Regen. Ther.* **2022**, *21*, 19–24. [[CrossRef](#)]
331. Gimona, M.; Brizzi, M.F.; Choo, A.B.H.; Dominici, M.; Davidson, S.M.; Grillari, J.; Hermann, D.M.; Hill, A.F.; de Kleijn, D.; Lai, R.C.; et al. Critical considerations for the development of potency tests for therapeutic applications of mesenchymal stromal cell-derived small extracellular vesicles. *Cytotherapy* **2021**, *23*, 373–380. [[CrossRef](#)]
332. Umezu, T.; Takanashi, M.; Murakami, Y.; Ohno, S.I.; Kanekura, K.; Sudo, K.; Nagamine, K.; Takeuchi, S.; Ochiya, T.; Kuroda, M. Acerola exosome-like nanovesicles to systemically deliver nucleic acid medicine via oral administration. *Mol. Ther. Methods Clin. Dev.* **2021**, *21*, 199–208. [[CrossRef](#)]
333. Fujita, Y.; Kadota, T.; Araya, J.; Ochiya, T.; Kuwano, K. Clinical Application of Mesenchymal Stem Cell-Derived Extracellular Vesicle-Based Therapeutics for Inflammatory Lung Diseases. *J. Clin. Med.* **2018**, *7*, 355. [[CrossRef](#)] [[PubMed](#)]
334. Urabe, F.; Kosaka, N.; Kimura, T.; Egawa, S.; Ochiya, T. Extracellular vesicles: Toward a clinical application in urological cancer treatment. *Int. J. Urol.* **2018**, *25*, 533–543. [[CrossRef](#)] [[PubMed](#)]
335. Liew, L.C.; Katsuda, T.; Gailhouste, L.; Nakagama, H.; Ochiya, T. Mesenchymal stem cell-derived extracellular vesicles: A glimmer of hope in treating Alzheimer's disease. *Int. Immunol.* **2017**, *29*, 11–19. [[CrossRef](#)] [[PubMed](#)]
336. Liu, X.; Zhang, G.; Yu, T.; He, J.; Liu, J.; Chai, X.; Zhao, G.; Yin, D.; Zhang, C. Exosomes deliver lncRNA DARS-AS1 siRNA to inhibit chronic unpredictable mild stress-induced TNBC metastasis. *Cancer Lett.* **2022**, *543*, 215781. [[CrossRef](#)] [[PubMed](#)]

337. Shan, S.; Chen, J.; Sun, Y.; Wang, Y.; Xia, B.; Tan, H.; Pan, C.; Gu, G.; Zhong, J.; Qing, G.; et al. Functionalized Macrophage Exosomes with Panobinostat and PPM1D-siRNA for Diffuse Intrinsic Pontine Gliomas Therapy. *Adv. Sci.* **2022**, *9*, e2200353. [[CrossRef](#)] [[PubMed](#)]
338. Subhan, M.A.; Torchilin, V.P. siRNA based drug design, quality, delivery and clinical translation. *Nanomedicine* **2020**, *29*, 102239. [[CrossRef](#)]
339. Zhang, Q.; Zhang, H.; Ning, T.; Liu, D.; Deng, T.; Liu, R.; Bai, M.; Zhu, K.; Li, J.; Fan, Q.; et al. Exosome-Delivered c-Met siRNA Could Reverse Chemoresistance to Cisplatin in Gastric Cancer. *Int. J. Nanomed.* **2020**, *15*, 2323–2335. [[CrossRef](#)]
340. Zhupanyan, P.; Ewe, A.; Büch, T.; Malek, A.; Rademacher, P.; Müller, C.; Reinert, A.; Jaimes, Y.; Aigner, A. Extracellular vesicle (ECV)-modified polyethylenimine (PEI) complexes for enhanced siRNA delivery in vitro and in vivo. *J. Control. Release* **2020**, *319*, 63–76. [[CrossRef](#)]
341. Nishida-Aoki, N.; Tominaga, N.; Takeshita, F.; Sonoda, H.; Yoshioka, Y.; Ochiya, T. Disruption of Circulating Extracellular Vesicles as a Novel Therapeutic Strategy against Cancer Metastasis. *Mol. Ther.* **2017**, *25*, 181–191. [[CrossRef](#)]
342. Zafarani, A.; Taghavi-Farahabadi, M.; Razizadeh, M.H.; Amirzargar, M.R.; Mansouri, M.; Mahmoudi, M. The Role of NK Cells and Their Exosomes in Graft Versus Host Disease and Graft Versus Leukemia. *Stem Cell Rev. Rep.* **2022**, *in press*. [[CrossRef](#)]
343. Fujii, S.; Miura, Y. Immunomodulatory and regenerative effects of MSC-derived extracellular vesicles to treat acute GVHD. *Stem Cells* **2022**, *in press*. [[CrossRef](#)]
344. Fujii, S.; Miura, Y.; Fujishiro, A.; Shindo, T.; Shimazu, Y.; Hirai, H.; Tahara, H.; Takaori-Kondo, A.; Ichinohe, T.; Maekawa, T. Graft-Versus-Host Disease Amelioration by Human Bone Marrow Mesenchymal Stromal/Stem Cell-Derived Extracellular Vesicles Is Associated with Peripheral Preservation of Naive T Cell Populations. *Stem Cells* **2018**, *36*, 434–445. [[CrossRef](#)] [[PubMed](#)]