Regulation of Extracellular Vesicle-Mediated Immune Responses against Antigen-Specific Presentation

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Abstract: Extracellular vesicles (EVs) produced by various immune cells, including B and T cells, macrophages, dendritic cells (DCs), natural killer (NK) cells, and mast cells, mediate intercellular communication and have attracted much attention owing to the novel delivery system of molecules in vivo. DCs are among the most active exosome-secreting cells of the immune system. EVs produced by cancer cells contain cancer antigens; therefore, the development of vaccine therapy that does not require the identification of cancer antigens using cancer-cell-derived EVs may have significant clinical implications. In this review, we summarise the molecular mechanisms underlying EV-based immune responses and their therapeutic effects on tumour vaccination.

Keywords: dendritic cells; extracellular vesicles; immune response; major histocompatibility complex; mesenchymal stem cell; microRNAs; tumour vaccination

1. Introduction

Extracellular vesicles (EVs) are lipid bilayer structures secreted by living cells and are classified into either exosomes, microvesicles (MVs), or apoptotic bodies, based on the intracellular production mechanism and size (Figure 1) [1–56]. Apoptotic bodies are released from apoptotic cells, whereas exosomes and MVs are released from healthy cells. Exosomes are endosomal membrane-derived vesicles, approximately 50–150 nm in size, formed during endocytosis and secreted by almost all types of cells, and are present in large numbers in body fluids such as blood, urine, cerebrospinal fluid, tears, and saliva. Their main constituents are lipids, proteins, and nucleic acids, including microRNAs (miRNAs), messenger RNA (mRNA), and DNA derived from secretory cells transferred to other cells [12,57–139]. Exosomes are involved in various physiological activities, such as immune regulation, neurodegeneration, and cancer development, as well as in the onset of disease mediated by intercellular communication involving the uptake of EVs into recipient cells [57,106,119,140–194]. Hence, preventive, diagnostic, and therapeutic strategies that target or use exosomes are likely to be effective and have significant potential in a clinical setting. Exosomes contain multivesicular body-related proteins, such as apoptosis-linked gene 2-interacting protein X (Alix); tumour susceptibility gene 101 (TSG101); the endosomal sorting complex required for transport complex (in late endosomes); heat shock proteins, such as HSP70 and HSP90; proteins involved in intracellular transport, such as Rab GTPase; and transmembrane protein family tetraspanins, such as CD9, CD61, and CD81, in addition to endosome membrane-derived lipids, such as cholesterol and sphingomyelin, whose expression levels differ based on the cell type from which they are secreted [195–199]. Exosomes are classified based on size; ~35 nm particles are referred to as exomeres, 60–80 nm
particles as small exosomes, and 90–120 nm particles as large exosomes [200–207], all of which exhibit different expression patterns for proteins, lipids, nucleic acids, and N-glycans.

**Figure 1.** Overview of EVs exosomes, microvesicles, and apoptotic bodies.

Conversely, MVs are vesicles with a wide range of sizes (100–1000 nm) and bud directly from the cell membrane into the outside of the cell [208,209]. Although MVs production mechanisms differ, many MVs are similar to exosomes, rendering them indistinguishable. Apoptotic bodies, micrometres in size, are particles in which apoptotic cells are displayed from the membrane and can be separated via low-speed centrifugation, hence are distinguishable from MVs and exosomes [210–213].

EVs are produced by various immune cells, including B and T cells, macrophages, dendritic cells (DC), natural killer (NK) cells, mast cells, and thymocytes [164,214–218] and are rich in proteins with immune functions, such as antigen-presenting molecules (major histocompatibility complex (MHC) class I, MHC class II, CD1), adhesion molecules (CD11b, intercellular adhesion molecule 1 (ICAM-1)), and co-stimulatory proteins (CD86) [219–222]. Additionally, exosomes are involved in releasing intracellular components to the outside of cells as waste products, and through their loaded immune-related molecules, they have various immune functions, such as antigen presentation, including the priming of early T cells, differentiation of mature T cells, development of effector functions, and regulation of immune-related cells [223–227].

Vaccine therapy is based on antigen presentation attributed to heightened immune function of EVs produced by DCs and antigen-presenting cells (APCs) [73,228–231]. Meanwhile, EVs produced by cancer cells contain cancer antigens; hence, the development of vaccine therapy that requires no identification of cancer antigens using cancer-cell-derived EVs is possible. EVs produced from mesenchymal stem cells (MSCs) have anti-inflammatory and tissue-regeneration properties, which may facilitate the development of immunotherapy [232–235]. Moreover, the development of novel immunotherapies that utilise EV characteristics, such as easy uptake by phagocytic cells or release from cells near target
tissues, is underway [236,237]. In this review, we summarise EV-based vaccine therapies and novel immunotherapies.

2. EV-Based Vaccine Therapy for Cancer

2.1. Immune Response via APCs with Functions of Chemokine

Cancer antigens and neoantigens can induce strong immune responses. When a cancer vaccine is administered, it is first taken up by APCs, including DCs that migrate to the lymph node, thereby activating antigen-specific T cells leading to the initiation of an immune response [238–240]. After undergoing positive and negative regulation, tumour-specific T cells exit the lymph node and migrate to the tumour site to eliminate cancer cells, although this process is strongly influenced by the immune environment created by the tumour [241–243]. In the cancer immune cycle, cancer antigens are released from cancer cells that have experienced cell death and are taken up by DCs [244,245]. These DCs mature, migrate to the lymph nodes, and present the captured cancer antigen to the MHCI molecules, thereby activating T cells [246–249], which in turn migrate and infiltrate the tumour tissue to recognise and eliminate tumour cells. The interaction between T cell-expressed integrin alpha L (LFA1) and ICAM-1 on the vascular endothelium initiates T cell infiltration into tumours that are suppressed by vascular endothelial growth factor A (VEGF-A), which is produced by cancer cells, further releasing new cancer antigens and continuing the cancer immune cycle [250–252]. In this process, the loss of beta-2 microglobulin, which is involved in the MHCI antigen presentation pathway in cancer cells, allows cancer cells to evade recognition by T cells [253–255]. Cancer cells in which beta-catenin signalling is activated have low chemokine (C-C motif) ligand 4 production and suppress the accumulation of conventional DC (cDC1), which produces chemokine (C-X-C motif) ligand 10 (CXCL10) in the tumour, thereby hindering T cell infiltration [256–258]. The deletion of the phosphatase and tensin homologue (Pten) in cancer cells suppresses T cell infiltration into the tumour site [259–261]. In this process, interferon-gamma (IFN-γ), produced by T and NK cells, suppresses tumour cell proliferation and enhances MHCI antigen presentation. Additionally, the M1 type of tumour-associated macrophages (TAMs) promotes anti-tumour immunity [262–264]. When cancer cells undergo immunogenic cell death, such as necrosis, high mobility group box 1, released at the same time as the antigen, acts on Toll-like receptors TLR2 and TLR4 on DCs to induce their maturation, leading to the efficient induction of anti-tumour immunity [265–267]. Among the DCs subsets within tumours, having a large amount of cDC1 is beneficial, since they take up cancer antigens from tumours and migrate to lymph nodes, in which chemokine expressions, such as CXCL9, 10, and CCL5, in the tumour and intratumoural environment induce stronger T cell migration and cross-prime CD8+ T cells [268–270]. Furthermore, NK cells in tumour tissues produce chemokines, such as CXCL1, CCL5, and FMS-like tyrosine kinase 3 ligands, which affect cDC1 [271]. The depletion of NK cells strongly suppresses the potentiation of immune checkpoint blockade action by interleukin (IL)-18, which regulates innate immunity, enhances the anti-tumour effect of immune checkpoint blockade through the induction of characteristic NK cells, which accumulate in the peritoneal cavity during early treatment prior to CD8+ T cells, and expresses CXCL1, whose depletion decreases the recruitment of CD103+ CXCR1+ cDCs to the peritoneum [272–274].

During antigen presentation by DCs, the expression of chemokine (C-C motif) receptor 7 (CCR7) on DCs induces migration to lymph nodes, where the chemokines CXCL13, CCL19, and CCL21 play a central role in adaptive immunity by exerting their effects via the actions of CXCL13 or CCL19 and CCL21 on receptors such as CXCR5 and CCR7, respectively [275–278]. These chemokines have two important functions in lymphocytes. First, interactions between CCL21, produced in the epithelial cells of lymph nodes, and CCR7, expressed on the surface of lymphocytes, activate integrins and induce adhesive responses. As a result, lymphocytes change shape and enter the lymph nodes through intercellular spaces that constitute high endothelial venules. Second, in the parenchyma of the lymph node, stromal cells secrete CCL19 and CCL21 around T cells, thereby promoting
the accumulation of T cells that strongly express CCR7 [279,280]. In contrast, CXCL13 expressed in the B cell region attracts B cells expressing CXCR5. These T and B cells in turn migrate along networks shaped by stromal cells, forming a 3D microenvironment within a lymph node, such as follicular DCs in B cell follicles and reticular fibroblasts in T cell areas.

In addition, the CD40/CD40L immune checkpoint pathway, which rescues tumour cells from apoptosis, prolongs survival and enhances the proliferation, activation, or maturation of APCs, including primarily macrophages and DCs, to produce IL-12 or IL-18 to stimulate NK cells. These, in turn, produce IFN-γ and express co-stimulatory molecules, such as CD80/CD86, ICAM-1, and CD44, which are required for the non-energetic full activation of T cells following T cell receptor stimulation [281,282].

Furthermore, regulatory T cells in lymph nodes interact with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), CD80, and CD86 on DCs to suppress T cell priming [283,284]. Anti-tumour immune responses are suppressed when cancer cells undergo tolerance-inducing cell death, such as apoptosis, during the release of cancer antigens [285]. Furthermore, cancer-associated fibroblasts (CAFs) create an immunosuppressive environment by remodelling the extracellular matrix of the tumour microenvironment [286–288]. In many cancer patients, one or more of these steps in the cycle are impaired, thereby preventing the induction of effective cancer immune responses.

2.2. EV Application of Vaccine Therapy

Therapy using EVs derived from cancer cells has gained popularity since it contains cancer antigens and induces a cancer antigen-specific immune response, which provides an anti-tumour effect [289]. Although inducing anti-tumour immunity using cancer-cell-derived EVs has been reported, the effect remains to be verified. Insufficient dynamic control of EVs and the low delivery efficiency to APCs, along with insufficient antigen presentation efficiency due to the effect of immunostimulatory agents, adjuvants, or low delivery efficiency to APCs remain major challenges. Pharmacokinetics analysis has shown that intravenously administered EVs derived from cancer cells accumulated in some tissues, such as the liver, spleen, and lungs. In the liver and spleen, it is taken up by macrophages and by vascular endothelial cells in the lungs [290,291]. Consequently, they are quick to disappear from the blood. Conversely, topical administration, which is frequently used in vaccine administration, showed that EVs are rapidly taken up by macrophages and other cells. Therefore, for the development of vaccine therapy using cancer-cell-derived EVs, it is necessary to control their kinetics, that is, continuous antigen delivery to DCs by imparting retention of EV at the administration site, thereby conferring tropism to DCs and controlling the intracellular dynamics of engulfed DC [7,292–295]. APCs, including DCs, are easy to use in large particles compared with other cell types.

Additionally, the disappearance of locally administered particles from the administration site is delayed as the size increases. This increase in size caused by EV formation aggregates may be used to confer APC tropism and retention at the administration site. The uptake of EV aggregates by DCs, in which EVs are linked by complementary strands of DNA, is increased by 2-fold, while the uptake into other cell types is reduced by approximately half. Furthermore, retention at the administration site following subcutaneous administration in mice has been shown to significantly increase due to aggregate formation. In mouse solid tumour models, EV aggregates are shown to induce anti-tumour immunity more efficiently than EVs and markedly delay tumour growth [296–298]. Therefore, EV aggregation is a useful kinetic control method to obtain the kinetics required for vaccine therapy.

3. Antigen Presentation through EVs Derived from Cancer Cells

DCs are among the most active exosome-secreting cells in the immune system, and they take up foreign substances such as bacteria that invade the body into phagosomes, fragment them into antigenic peptides, and activate T cells by placing them on MHC class II molecules, where are they presented on the cell surface [299,300]. In contrast, intracellular
antigenic peptides are presented by MHC class I molecules; however, exosomes secreted by DCs contain both MHC classes I and II. By binding to antigen-specific T cell receptors of CD8+ cytotoxic T cells and CD4+ helper T cells, T cells can be activated away from DCs (Figure 2). However, since the expression of co-stimulatory molecules, which are important for T cell activation, is lower on the exosome surface than DCs surface, the activation is as low as 5–10% compared with cases where DCs are activated by direct contact with T cells. Furthermore, by carrying antigen peptide/MHC complexes, exosomes not only play a direct antigen-presenting function but deliver exosomes into other APCs. It is also possible to indirectly promote antigen presentation by passing antigens to MHC molecules within cells [301–303]. When antigens are presented by DCs that have endocytosed EVs derived from cancer cells, they are presented to MHC class II by degradation of the antigenic protein by endosomes, and to the MHC class I by degradation of the antigenic protein in the cytoplasm. In contrast, exosomes derived from phagocytic cells, such as macrophages, contain antigens derived from phagocytosed bacteria; it is possible to promote the efficient activation of T cells by transferring the antigen to DCs with stronger antigen-presenting ability via exosomes. When considering cancer therapy, the induction of cell-mediated immunity is desirable, where antigen presentation to MHC class I is important for this purpose. The escape of EVs from endosomes is useful for delivering endocytosed proteins to the cytoplasm, hence modifying cancer-cell-derived EVs with GALA peptide, a 30-amino-acid synthetic peptide with a glutamic acid–alanine–leucine–alanine (EALA) repeat, exerts a membrane-disrupting ability in a low-pH environment. Morishita et al. effectively illustrated the possibility to destroy lipid membranes at low pH, escape endosomes in engulfed DCs, and efficiently present cancer-cell-derived antigens to MHC class I on DCs [304–306]. Thus, GALA modification promotes the transport of exosome inclusions into the cytoplasm and enhances the MHC class I presentation of cancer antigens based on the control of intracellular dynamics. Therefore, since cancer-cell-derived exosomes contain cancer antigens and can induce anti-tumour immune responses, they can be used as novel cancer vaccine formulations without the identification of cancer antigens. Furthermore, DC directivity can be conferred by a DC-directing ligand. To transfer CD40L to the surface of cancer-cell-derived EVs, a CD40L-LA (Lactadherin) fusion protein in which LA has an affinity for phosphatidylserine, a lipid present in the EV membrane, was used. Liu et al. revealed that CD40L-modified EVs show an increased ability to activate DCs than unmodified EVs [307].
which present antigens circulating in the bloodstream and improve disease conditions and enter the patient, they present antigens to naïve T cells. CD8+ naïve T cells are activated to differentiate into cytotoxic T cells, which results in antigen-specific antitumour activity. Conversely, CD4+ naïve T cells differentiate into helper T cells to assist cytotoxic T cells, which present antigens circulating in the bloodstream and improve disease conditions and the suppression of disease progression, even in patients with distant metastases. Further, some anti-tumour effects of DCs are retained in memory T cells. The activation of DCs that have taken up cancer antigens is important for the induction of cancer antigen-specific immune responses. Therefore, developing a method to deliver cancer-cell-derived EVs and adjuvants to the same DCs will have significant therapeutic implications. The modification of cancer-cell-derived exosomes containing cancer antigens with an adjuvant induces potent anti-tumour immunity through the simultaneous delivery of cancer antigens and adjuvants to DCs. Morishita et al. reported that cancer-cell-derived EVs were modified with an SAV-LA fusion protein between biotin-binding protein streptavidin (SAV) and LA, reacting with a biotin derivative of CpG DNA, an immunostimulatory nucleic acid [310]. This nucleic

**Figure 2.** EV-mediated antigen presentation to CD4+ helper or CD8+ cytotoxic T cells from dendritic cells. DC-derived EVs, which can migrate to tumours or the spleen directly or indirectly present antigens to CD4+ helper and CD8+ cytotoxic T cells via MHC molecules, thereby inducing immune responses. Red triangle: antigen peptide.

### 4. Antigen-Specific Immune Response in Cancer

The immune response that eliminates foreign substances such as bacteria and viruses does not attack host cells. This mechanism, referred to as “autoimmune tolerance”, is induced by eliminating harmful cells such as cancer cells and unnecessary cells in the body by phagocytes, such as macrophages and DCs [308,309]. This process prevents dead cells from releasing harmful substances and helps the surrounding tissues to maintain normal function.

However, if the elimination of dead cells is delayed, or the types of cells that eat dead cells change, immune tolerance breaks down. Cancer vaccines for cancer immunotherapy are composed of cancer antigens and adjuvants, which induce antigen-specific cytotoxic T cells through APC presentation and promote the exclusion of cancer cells. When DCs that differentiate in vitro are loaded with tumour antigens and reinjected into the patient, they present antigens to naïve T cells. CD8+ naïve T cells are activated to differentiate into cytotoxic T cells, which results in antigen-specific antitumour activity. Conversely, CD4+ naïve T cells differentiate into helper T cells to assist cytotoxic T cells, which present antigens circulating in the bloodstream and improve disease conditions and the suppression of disease progression, even in patients with distant metastases. Further, some anti-tumour effects of DCs are retained in memory T cells. The activation of DCs that have taken up cancer antigens is important for the induction of cancer antigen-specific immune responses. Therefore, developing a method to deliver cancer-cell-derived EVs and adjuvants to the same DCs will have significant therapeutic implications. The modification of cancer-cell-derived exosomes containing cancer antigens with an adjuvant induces potent anti-tumour immunity through the simultaneous delivery of cancer antigens and adjuvants to DCs. Morishita et al. reported that cancer-cell-derived EVs were modified with an SAV-LA fusion protein between biotin-binding protein streptavidin (SAV) and LA, reacting with a biotin derivative of CpG DNA, an immunostimulatory nucleic acid [310]. This nucleic
acid has attracted attention as an adjuvant consisting of unmethylated cytosine and guanine (CpG), frequently present in the genomic DNA (CpG-DNA) of bacteria and viruses for host defence in mammalian innate immunity, in which two sequences, K type and D type, are particularly effective for CpG-DNA. The K type mainly induces the proliferation of B cells and production of cytokines such as IL-6, while the D type induces the production of the type I interferon from plasmacytoid DCs. The mechanism underlying immune activation involves the binding of CpG-DNA to TLR9 in the endosome, which induces the nuclear factor kappa B (NF-κB) pathway through the adaptor molecule myeloid differentiation primary response gene 88, thereby inducing the production of various cytokines [311–313].

When CpG DNA-modified EV was added, uptake into DCs increased compared to the addition of CpG DNA alone. Therefore, CpG DNA modification of EVs enables the simultaneous delivery of cancer antigens and adjuvant CpG DNA to the same cell [308]. Additionally, DCs supplemented with CpG DNA-modified EVs showed a higher cytokine production than those with CpG DNA or EVs alone. Furthermore, in an in vivo experimental system using tumour-bearing mouse models, CpG DNA-modified EVs can induce cancer antigen-specific cellular and humoral immune responses and significantly suppress tumour growth and metastasis to the lungs, thereby prolonging survival [314–316]. Therefore, the CpG DNA modification of cancer-cell-derived EVs enables the simultaneous delivery of cancer antigen and adjuvants to the same DCs and the induction of anti-tumour immunity.

5. DC-Derived EVs as Prospective Vaccines

DCs, which serve as a link between innate and adaptive immunity, are involved in the initiation and suppression of immune responses. Antigen presentation to naïve cytotoxic and helper T cells is performed through MHC classes I and II molecules, respectively. Molecules contained in DC-derived EVs are MHC class I/II and CD86 proteins, which are capable of mediating antigen presentation to CD8+ and CD4+ T cells and the subsequent proliferation of T cells [317].

CD1a, b, c, or d proteins are involved in the presentation of lipid antigens, while ICAM-1 plays an important role in regulating DC-T cell communication, where ICAM-1 can either promote the uptake of DC-derived EVs by target DCs or the interaction of T cells with DCs that retain DC-derived EVs on their outer surface as ligands for Mac1 integrin (CD11b/CD18) and lymphocyte function-associated antigen 1 (LFA1, CD11a/CD18). Additionally, DC-derived EVs are rich in tetraspanins, including CD9, CD37, CD53, CD63, CD81, and CD82, which regulate DC interactions. Thus, DC-derived EVs can induce cellular and humoral immunity by antigen presentation via DCs that have incorporated them. A clinical trial for vaccine therapy using DC-derived EVs has been conducted, showing that although its safety has been confirmed, its therapeutic effect is limited. Ovalbumin (OVA) has been previously used as a model antigen; EVs were recovered from DCs spiked with OVA, along with LPS and IFN-γ as activators of DCs, where it carried OVA, in addition to MHC class I, antigen presentation, and co-stimulatory molecules such as CD86 [318–320]. As DC-derived EVs have a strong ability to activate immune cells, the addition of macrophages and DCs further exacerbates the activation of these cells. These DC-derived EV-loaded DCs can present antigens to T cells, while the DC-derived EVs can directly present antigens to T cells. Furthermore, the administration of DC-derived EVs to tumour-bearing model mice, established by transplanting OVA-expressing cancer cells, induced cellular and humoral immunity specific to the loaded OVA antigen thereby displaying anti-tumour effects. Thus, EVs recovered from activated DCs have properties that contribute to vaccine therapy, while the optimisation of the activation state of DCs may produce EVs with enhanced activity.

6. Application of MSC-Derived EVs in Modulating the Immune Response

MSCs are fibroblast-like progenitor cells recovered from the bone marrow, adipose tissue, and umbilical cord. They have adipogenic, chondrogenic, and osteogenic differentiation potential [321–328]. MSCs do not express human leukocyte antigen (HLA) class II
antigens; therefore, they are not only less immunogenic in allogeneic transplantation but are also capable of suppressing the function of various immune cells. To date, clinical trials have been conducted using MSCs as novel therapeutic agents to treat various diseases, including acute diseases, such as ischaemic stroke and myocardial infarction. MSCs are also intended anti-inflammatory therapy for diseases caused by uncontrolled inflammatory reactions, such as acute graft-versus-host disease (GvHD) and Crohn’s disease [329–332].

Initially, MSCs were characterised by their cell differentiation potential and their direct interaction with immune cells. However, it has become clear that the immunoregulatory ability of MSCs is based on paracrine action; EVs containing marker proteins, such as CD9, CD81, and ALIX, at approximately 100 nm from MSC culture supernatant have therapeutic effects on disease model mice. Furthermore, in a clinical trial where EVs recovered from steroid-refractory GvHD patients, increasing the dose of MSC-derived EVs resulted in a long-term reduction in GvHD symptoms and reduced steroid dose. The addition of MSC-derived EVs to patient-derived peripheral blood cells suppressed the secretion of the inflammatory cytokines IL-1β, tumour necrosis factor-alpha (TNFα), and IFNγ [333]. Moreover, MSC-derived EVs comprised anti-inflammatory cytokines, transforming growth factor-β (TGF-β), IL-10, and HLA-G, further improving GvHD symptoms and chronic kidney disease. Notably, the levels of TGF-β and IL-10 in peripheral blood were significantly elevated relatively early following administration of MSC-derived EVs, and their levels remained high even after one year. Conversely, the inflammatory cytokine TNFα was significantly suppressed by the administration of MSC-derived EVs.

In addition to GvHD, MSC therapy may be clinically applied to other diseases such as severe heart failure and type I diabetes [334–337]. The administration of MSCs improves heart failure in the disease model mice, and adiponectin produced by adipocytes increases the exosomes produced by MSCs, thereby promoting their therapeutic effects. Furthermore, in a mouse model that developed diabetes by inhibiting the binding of Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1 (PD-L1), immune cell infiltration into the space between pancreatic insulin-producing cells was observed using immune checkpoint inhibitors. In particular, there was a marked increase in cytotoxic macrophages that destroyed pancreatic insulin-producing cells. The administration of human adipose tissue-derived MSCs to these mice suppressed the infiltration of immune cells and the onset of diabetes. Furthermore, following the administration of MSCs, a marked increase in MSC-derived exosomes in the blood of mice was observed, suggesting that humoral factors such as exosomes may be involved in the suppression of diabetes development. The infiltration of immune cells, such as cytotoxic macrophages, was also observed in human islets following the administration of immune checkpoint inhibitors. Thus, humoral factors, such as exosomes produced by human adipose tissue-derived MSCs, suppress the onset of type 1 diabetes induced by immune checkpoint inhibition.

7. EV-Based Immunotherapy

7.1. Immune-Related Molecules Loaded into Exosomes

EVs not only contain protein antigens but also secretory cell-derived mRNAs and non-coding RNAs, and their functions have attracted much attention. These RNAs are protected by the lipid bilayer membrane of exosomes, and thus are not degraded by RNases and remain stable in the blood and body fluids. While there are RNAs detected in both exosomes and their secreting cells, there are others that can only be detected in either, suggesting the existence of a mechanism to selectively incorporate specific RNAs into exosomes taken up by target cells fused with the endosomal membrane. This releases trapped RNA into the target cell cytoplasm. In this study, the released mRNAs are translated into proteins, miRNAs suppress the translation of target genes, while exosomes regulate gene expression in target cells. Immune cells that encounter a foreign object horizontally transmit their activation state to cells that have not yet encountered it through RNA. In addition, various immune-related molecules are loaded into exosomes, which in turn regulate the immune responses. For example, exosomes derived from cytotoxic T cells
and NK cells carry TNF family proteins, such as Fas ligand, TRAIL, and CD40 ligand, and induce apoptosis in target cells [338]. Similarly, some cancer cells release exosomes loaded with the Fas ligand and TRAIL, which induce apoptosis in immune cells, thereby escaping immune attack. The TNF family proteins are produced in a membrane-bound form and cleaved by a membrane-type metalloprotease to become soluble. Apoptosis-inducing activity is mainly mediated by the membrane form, while the activity of the soluble form is weak. Moreover, TNF family proteins on exosomes are stable without being cleaved by membrane metalloproteases and have strong apoptosis-inducing activity by forming trimers through the membrane. The exosome-mediated transport of TNF family proteins is involved in the development of various inflammatory and autoimmune diseases. For example, exosomes released from synovial fibroblasts of patients with rheumatoid arthritis accumulate high concentrations of membrane-bound TNF-α, exacerbating the pathology of rheumatoid arthritis [339,340]. Further, cancer-cell-derived exosomes have various immunosuppressive effects in addition to inducing apoptosis in immune cells. For example, exosomes suppress the expression of the NKG2D receptor in NK cells, which is involved in the recognition mechanism of cancer cells and reduces cancer cytotoxicity [341–344].

In contrast, when cancer-cell-derived exosomes are taken up by monocytes, the effects of TGF-β and prostaglandin E2 contained in the exosomes induce the differentiation of monocytes into bone-marrow-derived immunosuppressive cells, which release various immunosuppressive molecules such as IL-10, thereby promoting the inactivation of immunocompetent cells and the induction of regulatory T cells to suppress anti-tumour immunity [345]. Through these mechanisms, cancer cells may suppress the functions of the immune cells that attack them and promote cancer progression.

7.2. EV-Mediated Cytokine Enhancement and Tumour Progression

Cytokines are paracrine factors involved in the immune system where EV-mediated cytokine enhancement has been reported. For example, IFN-γ bound to its receptor on the EV surface stimulates target cells more efficiently than IFN-γ alone. Additionally, for the antagonism of CD47, a “Not Eat Me” signal is overexpressed on the surface of most tumours by a signal-regulatory protein alpha. This protein is expressed on phagocytic cells that interact with CD47-bearing EVs, inhibiting CD47 on cancer cells and thereby increasing cancer cell phagocytosis and inducing anti-tumour T-cell responses [346–349]. Additionally, EVs have been shown to evade immune clearance better than artificial liposomes, likely due to the expression of CD47 on exosomal membranes. Furthermore, CD47 is overexpressed in tumours where its expression is associated with poor progression-free survival and inversely correlated with macrophage infiltration in tumour tissues loaded on exosomes, thereby promoting tumour immune evasion. The inhibition of exosome secretion or uptake via the knockdown of RAB27A, a regulator of exosome secretion, reduces the expression of CD47 in tumour cells, promotes phagocytosis by M1 macrophages in tumour tissues, and suppresses tumour progression [348]. siRNA-loaded exosomes are selectively taken up by pancreatic tumour cells, which is facilitated by enhanced micropinocytosis. This reduces oncogenic KRAS signalling and suppresses tumour growth in multiple mouse models of pancreatic cancer [349]. Therefore, increasing cancer cell phagocytosis by antagonising CD47 signalling with EVs may be an effective approach for cancer immunotherapy. Furthermore, anti-PD-L1 therapy using platelets and platelet-derived EVs has also been reported, where the PD-L1 monoclonal antibody is bound to the surface of platelets [350,351]. When these platelets are intravenously administered, they become activated and release EVs into tumour tissue. In contrast, anti-PD-L1-bound platelets are activated in the tumour microenvironment and release anti-PD-L1-bound EVs, which inhibit immune checkpoints in tumour tissue, thereby increasing the number of infiltrating CD8+ and CD4+ T cells within the tumour. In addition, the number of CD4+ Foxp3+ T cells was reduced, while the proliferation of CD8+ and CD4+ effector T cells within the tumour was enhanced. Furthermore, the administration of anti-PD-L1 antibody-conjugated platelets suppressed cancer growth and metastasis in tumour-bearing mice and significantly prolonged their
survival. This suggests that platelet-secreted EVs are effective delivery carriers that inhibit immune checkpoint molecules. In addition, based on the susceptibility of EVs to macrophage uptake, anti-inflammatory therapy has been reported by loading EVs with the NF-κB binding domain (NBD), an inhibitory peptide of NF-κB, which is a transcriptional factor that promotes inflammation and delivers EVs to macrophages [352–354]. For this strategy, a fusion protein is prepared in which Gag, an EV inner-membrane tropic protein, is fused with NBD. The addition of Gag-NBD-loaded EVs to LPS-stimulated macrophages significantly suppressed macrophage inflammatory responses, that is, inflammatory cytokine production, nitric oxide (NO) synthase induction, and subsequent NO production [355,356]. Therefore, EVs-mediated immune responses are essential factors for tumour progression.

8. Conclusions

EVs derived from cancer cells contain cancer antigens, and their administration induces a cancer antigen-specific immune response, thereby exerting an anti-tumour effect. Therapeutic studies using mouse solid tumour models have shown that EV aggregates can induce anti-tumour immunity more efficiently than EVs alone and markedly delay tumour growth. When cancer-cell-derived exosomes are taken up by monocytes, the TGF-β and prostaglandin E2 contained in the exosomes induce the differentiation of monocytes into bone-marrow-derived immunosuppressive cells, which in turn release various immunosuppressive molecules, such as IL-10, thereby promoting the inactivation of immunocompetent cells and the induction of regulatory T cells to suppress anti-tumour immunity. Understanding the molecular mechanisms in which EVs-mediated immunosuppression will help to develop a novel therapeutic strategy against cancers.

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References

1. Shefer, A.; Yalovaya, A.; Tamkovich, S. Exosomes in Breast Cancer: Involvement in Tumor Dissemination and Prospects for Liquid Biopsy. *Int. J. Mol. Sci.* 2022, 23, 8845. [CrossRef]
2. Gul, B.; Syed, F.; Khan, S.; Iqbal, A.; Ahmad, I. Characterization of extracellular vesicles by flow cytometry: Challenges and promises. *Micron* 2022, 161, 10341. [CrossRef]
3. Hermann, D.M.; Xin, W.; Bähr, M.; Giebel, B.; Doepnner, T.R. Emerging roles of extracellular vesicle-associated non-coding RNAs in hypoxia: Insights from cancer, myocardial infarction and ischemic stroke. *Theranostics* 2022, 12, 5776–5802. [CrossRef]
4. Khan, F.H.; Reza, M.J.; Shao, Y.F.; Perwez, A.; Zahra, H.; Dowlati, A.; Abbas, A. Role of exosomes in lung cancer: A comprehensive insight from immunomodulation to theragnostic applications. *Biochim. Biophys. Acta Rev. Cancer* 2022, 1877, 188776. [CrossRef] [PubMed]
5. Tamura, T.; Yoshioka, Y.; Sakamoto, S.; Ichikawa, T.; Ochiya, T. Extracellular vesicles in bone homeostasis: Key roles of physiological and pathological conditions. *J. Bone Miner. Metab.* 2022, in press. [CrossRef]
6. De Sousa, K.P.; Rossi, L.; Abdullahi, M.; Ramírez, M.I.; Stratton, D.; Inal, J.M. Isolation and characterization of extracellular vesicles and future directions in diagnosis and therapy. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 2022, 27, e1835. [CrossRef] [PubMed]
7. Ng, C.Y.; Kee, L.T.; Al-Masawa, M.E.; Lee, Q.H.; Subramaniam, T.; Kok, D.; Ng, M.H.; Law, J.X. Scalable Production of Extracellular Vesicles and Its Therapeutic Values: A Review. *Int. J. Mol. Sci.* 2022, 23, 7986. [CrossRef]
8. Procyk, G.; Bilicki, D.; Balsam, P.; Lodziński, P.; Grabowski, M.; Gaśecka, A. Extracellular Vesicles in Atrial Fibrillation-State of the Art. *Int. J. Mol. Sci.* 2022, 23, 7591. [CrossRef]
9. Ramos-Zaldívar, H.M.; Polakovicova, I.; Salas-Huenuelo, 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] [PubMed]
10. Zhou, L.; Luo, H.; Lee, J.W. Role of extracellular vesicles in lung diseases. *Chin. Med. J. 2022, in press.* [CrossRef]
11. Arifin, D.R.; Wittwer, K.W.; Bulte, J.W.M. Non-Invasive imaging of extracellular vesicles: Quo vadis in vivo? *J. Extracell. Vesicles* 2022, 11, e12241. [CrossRef]

12. Zeng, Y.; Qiu, Y.; Jiang, W.; Shen, J.; Yao, X.; He, X.; Li, L.; Fu, B.; Liu, X. Biological Features of Extracellular Vesicles and Challenges. *Front. Cell Dev. Biol.* 2022, 10, 816698. [CrossRef] [PubMed]

13. Kee, L.T.; Ng, C.Y.; Al-Masawa, M.E.; Foo, J.B.; How, C.W.; Ng, M.H.; Law, J.X. Extracellular Vesicles in Facial Aesthetics: A Review. *Int. J. Mol. Sci.* 2022, 23, 6742. [CrossRef]

14. Matsuzaka, Y.; Yashiro, R. Therapeutic Strategy of Mesenchymal-Stem-Cell-Derived Extracellular Vesicles as Regenerative Medicine. *Int. J. Mol. Sci.* 2022, 23, 6480. [CrossRef]

15. Vinaïphat, A.; Sze, S.K. Proteomics for comprehensive characterization of extracellular vesicles in neurodegenerative disease. *Exp. Neurol.* 2022, 355, 114149. [CrossRef]

16. Han, C.; Qin, G. Reporter Systems for Assessments of Extracellular Vesicle Transfer. *Front. Cardiovasc. Med.* 2022, 9, 922420. [CrossRef]

17. Suades, R.; Greco, M.F.; Padró, T.; Badimon, L. Extracellular Vesicles as Drivers of Immunoinflammation in Atherothrombosis. *Cells* 2022, 11, 1845. [CrossRef]

18. Trisko, J.; Fleck, J.; Kau, S.; Oesterreicher, J.; Holntherner, W. Lymphatic and Blood Endothelial Extracellular Vesicles: A Story Yet to Be Written. *Life* 2022, 12, 654. [CrossRef]

19. Anusha, R.; Priya, S. Dietary Exosome-Like Nanoparticles: An Updated Review on Their Pharmacological and Drug Delivery Applications. *Mol. Nutr. Food Res.* 2022, 66, e2200142. [CrossRef]

20. Vafaei, S.; Mansoori, M.; Hashemi, F.; Basiri, M. Exosome Odyssey to Original Line in Dental Regeneration. *J. Oral. Biosci.* 2022, 64, 271–278. [CrossRef]

21. Ginini, L.; Billan, S.; Fridman, E.; Gil, Z. Insight into Extracellular Vesicle-Cell Communication: From Cell Recognition to Intracellular Fate. *Cells* 2022, 11, 1375. [CrossRef]

22. Yang, J.; Shin, T.S.; Kim, J.S.; Jee, Y.K.; Kim, Y.K. A new horizon of precision medicine: Combination of the microbiome and extracellular vesicles. *Exp. Mol. Med.* 2022, 54, 466–482. [CrossRef]

23. Wu, Q.; Duan, W.Z.; Chen, J.B.; Zhao, X.P.; Li, X.J.; Liu, Y.Y.; Ma, Q.Y.; Xue, Z.; Chen, J.X. Extracellular Vesicles: Emerging Roles in Developing Therapeutic Approach and Delivery Tool of Chinese Herbal Medicine for the Treatment of Depressive Disorder. *Front. Pharmacol.* 2022, 13, 843412. [CrossRef]

24. Bagci, C.; Sever-Bahçekapili, M.; Belder, N.; Bennett, A.P.S.; Erdener, Ş.E.; Dalkara, T. Overview of extracellular vesicle characterization techniques and introduction to combined reflectance and fluorescence confocal microscopy to distinguish extracellular vesicle subpopulations. *Neurophotonics* 2022, 9, 021903. [CrossRef] [PubMed]

25. Beck, S.; Hochreiter, B.; Schmid, J.A. Extracellular Vesicles Linking Inflammation, Cancer and Thrombotic Risks. *Front. Cell Dev. Biol.* 2022, 10, 859863. [CrossRef] [PubMed]

26. Tan, Y.; Tang, F.; Li, J.; Yu, H.; Wu, M.; Wu, Y.; Zeng, H.; Hou, K.; Zhang, Q. Tumor-derived exosomes: The emerging orchestrators in melanoma. *Biomed. Pharmacother.* 2022, 149, 112832. [CrossRef] [PubMed]

27. Shan, C.; Liang, Y.; Cai, H.; Wang, F.; Chen, X.; Yin, Q.; Wang, K.; Wang, Y. Emerging function and clinical significance of extracellular vesicle noncoding RNAs in lung cancer. *Mol. Ther. Oncolytics* 2022, 24, 814–833. [CrossRef] [PubMed]

28. Mun, D.; Oh, S.; Kim, Y. Perspectives on Bovine Milk-Derived Extracellular Vesicles for Therapeutic Applications in Gut Health. *Food Sci. Anim. Resour.* 2022, 42, 197–209. [CrossRef]

29. Nafar, S.; Nouri, N.; Alipour, M.; Fallahi, J.; Zare, F.; Tabei, S.M.B. Exosome as a target for cancer treatment. *J. Investig. Med.* 2022, 70, 1212–1218. [CrossRef]

30. Hua, Y.; Chang, X.; Fang, L.; Wang, Z. Subgroups of Extracellular Vesicles: Can They Be Defined by “Labels”? DNA Cell Biol. 2022, 41, 249–256. [CrossRef]

31. Berezin, A.E.; Berezin, A.A. Extracellular Vesicles and Thrombogenicity in Atrial Fibrillation. *Int. J. Mol. Sci.* 2022, 23, 1774. [CrossRef]

32. Soler-Botija, C.; Monguíó-Tortajada, M.; Munizaga-Larroudé, M.; Gálvez-Montón, C.; Bayes-Genis, A.; Roura, S. Mechanisms governing the therapeutic effect of mesenchymal stromal cell-derived extracellular vesicles: A scoping review of preclinical evidence. *Biomed. Pharmacother.* 2022, 147, 112683. [CrossRef]

33. Araujo-Abad, S.; Saceda, M.; de Juan Romero, C. Biomedical application of small extracellular vesicles in cancer treatment. *Adv. Drug Deliv. Rev.* 2022, 182, 114117. [CrossRef] [PubMed]

34. Zhou, Z.W.; Zheng, W.; Xiang, Z.; Ye, C.S.; Yin, Q.Q.; Wang, S.H.; Xu, C.A.; Wu, W.H.; Hui, T.C.; Wu, Q.Q.; et al. Clinical implications of exosome-derived noncoding RNAs in liver. *Lab. Invest.* 2022, 102, 464–473. [CrossRef] [PubMed]

35. Ding, X.; Wang, X.; Du, J.; Han, Q.; Zhang, D.; Zhu, H. A systematic review and Meta-analysis of urinary extracellular vesicles proteome in diabetic nephropathy. *Front. Endocrinol.* 2022, 13, 866252. [CrossRef] [PubMed]

36. Fujita, Y. Extracellular vesicles in idiopathic pulmonary fibrosis: Pathogenesis and therapeutics. *Inflamm. Regen.* 2022, 42, 23. [CrossRef]

37. Muñozes, G.; Sipos, F. Mesenchymal Stem Cell-Derived Secretome: A Potential Therapeutic Option for Autoimmune and Immune-Mediated Inflammatory Diseases. *Cells* 2022, 11, 2300. [CrossRef]

38. Liu, G.; Yin, X.M. The Role of Extracellular Vesicles in Liver Pathogenesis. *Am. J. Pathol.* 2022, 192, 1358–1367. [CrossRef]
39. Georgatzakou, H.T.; Fortis, S.P.; Papageorgiou, E.G.; Antonelou, M.H.; Kriberardis, A.G. Blood Cell-Derived Microvesicles in Hematological Diseases and beyond. *Biomolecules* **2022**, *12*, 803. [CrossRef]

40. Abbassazadeh, H.; Ghorbani, F.; Abbaspour-Aghdam, S.; Kamrani, A.; Valizadeh, H.; Nadiri, M.; Sadeghi, A.; Shamsasenjan, K.; Jadidi-Niaragh, F.; Roshangar, L.; et al. Chronic obstructive pulmonary disease and asthma: Mesenchymal stem cells and their extracellular vesicles as potential therapeutic tools. *Stem Cell Res. Ther.* **2022**, *13*, 262. [CrossRef]

41. Wei, W.; Pan, Y.; Yang, X.; Chen, Z.; Heng, Y.; Yang, B.; Pu, M.; Zuo, J.; Lai, Z.; Tang, Y.; et al. The Emerging Role of the Interaction of Extracellular Vesicle and Autophagy-Novel Insights into Neurological Disorders. *J. Inflamm. Res.* **2022**, *15*, 3395–3407. [CrossRef]

42. Frommeyer, T.C.; Gilbert, M.M.; Brittain, G.V.; Wu, T.; Nguyen, T.Q.; Rohan, C.A.; Travers, J.B. UBV-Induced Microvesicle Particle Release and Its Effects on the Cutaneous Microenvironment. *Front. Immunol.* **2022**, *13*, 880850. [CrossRef]

43. 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]

44. Neri, T.; Celi, A.; Tinè, M.; Bernardinello, N.; Cosio, M.G.; Saetta, M.; Nieri, D.; Bazzan, E. The Emerging Role of Extracellular Vesicles Detected in Different Biological Fluids in COPD. *Int. J. Mol. Sci.* **2022**, *23*, 5136. [CrossRef] [PubMed]

45. Li, Y.; Zhao, W.; Wang, Y.; Wang, H.; Liu, S. Extracellular vesicle-mediated crosstalk between pancreatic cancer and stromal cells in the tumor microenvironment. *J. Nanobiotechnol.* **2022**, *20*, 208. [CrossRef]

46. Gangadaran, P.; Rajendran, R.L.; Kwack, M.H.; Jeyaraman, M.; Hong, C.M.; Sung, Y.K.; Ahn, B.C. Application of Cell-Derived Extracellular Vesicles for Immunomodulation in Tissue Regeneration. *Stem Cell Res. Ther.* **2022**, *13*, 262. [CrossRef] [PubMed]

47. Zhao, Z.; Guo, N.; Chen, W.; Wang, Z. Leveraging Extracellular Non-coding RNAs to Diagnose and Treat Heart Diseases. *J. Cardiovasc. Transl. Res.* **2022**, *15*, 456–468. [CrossRef] [PubMed]

48. Gomez, N.; James, V.; Onion, D.; Fairclough, L.C. Extracellular vesicles and chronic obstructive pulmonary disease (COPD): A systematic review. *Respir. Res.* **2022**, *23*, 82. [CrossRef]

49. Wang, Y.; Xu, H.; Wang, J.; Yi, H.; Song, Y. Extracellular Vesicles in the Pathogenesis, Treatment, and Diagnosis of Spinal Cord Injury: A Mini-Review. *Curr. Stem Cell Res. Ther.* **2022**, *17*, 317–327. [CrossRef]

50. Muhammad, S.A.; Abbas, A.Y.; Imam, M.U.; Saidu, Y.; Biblis, L.S. Efficacy of stem cell secretome in the treatment of traumatic brain injury: A systematic review and meta-analysis of preclinical studies. *Mol. Neurobiol.* **2022**, *59*, 2894–2909. [CrossRef]

51. Gabisonia, K.; Khan, M.; Recchia, F.A. Extracellular vesicle-mediated bidirectional communication between heart and other organs. *Am. J. Physiol. Heart Circ. Physiol.* **2022**, *322*, H769–H784. [CrossRef] [PubMed]

52. Piening, L.M.; Wachs, R.A. Matrix Bound Nanovesicles: What are they and what do they do? *Cells Tissues Organs* **2022**, *in press*. [CrossRef]

53. Sabaratnam, R.; Wojtaszewski, J.F.P.; Højlund, K. Factors mediating exercise-induced organ crosstalk. *Acta. Physiol.* **2022**, *234*, e13766. [CrossRef] [PubMed]

54. Al-Koussa, H.; AlZaim, I.; El-Sabban, M.E. Pathophysiology of Coagulation and Emerging Roles for Extracellular Vesicles in Coagulation Cascades and Disorders. *J. Clin. Med.* **2022**, *11*, 4932. [CrossRef]

55. Marki, A.; Ley, K. The expanding family of neutrophil-derived extracellular vesicles. *Immunol. Rev.* **2022**, *in press*. [CrossRef]

56. Yari, H.; Mikhailova, M.V.; Mardasi, M.; Jafarzadehgharehziaddin, M.; Shahrokh, S.; Thangavelu, L.; Ahmadi, H.; Shamoli, N.I.; Yaghoubi, Y.; Zamani, M.; et al. Emerging role of mesenchymal stromal cells (MSCs)-derived exosome in neurodegeneration-associated conditions: A groundbreaking cell-free approach. *Stem Cell Res. Ther.* **2022**, *13*, 423. [CrossRef] [PubMed]

57. Pischutta, F.; Caruso, E.; Cavaleiro, H.; Salgado, A.J.; Loane, D.J.; Zanier, E.R. Mesenchymal stromal cell secretome for traumatic brain injury: Focus on immunomodulatory action. *Exp. Neurol.* **2022**, *357*, 114199. [CrossRef] [PubMed]

58. Wang, Z.; Zhao, Z.; Gao, B.; Zhang, L. Exosome mediated biological functions within skeletal microenvironment. *Front. Bioeng. Biotechnol.* **2022**, *10*, 953916. [CrossRef]

59. Gangadaran, P.; Rajendran, R.L.; Kwack, M.H.; Jeyaraman, M.; Hong, C.M.; Sung, Y.K.; Ahn, B.C. Application of Cell-Derived Extracellular Vesicles and Engineered Nanovesicles for Hair Growth: From Mechanisms to Therapeutics. *Front. Cell Dev. Biol.* **2022**, *10*, 632787. [CrossRef]

60. Li, J.; Zhang, Y.; Luo, B. Effects of Exosomal Viral Components on the Tumor Microenvironment. *Cancers* **2022**, *14*, 3552. [CrossRef]

61. Imanbekova, M.; Suarasan, S.; Lu, Y.; Jurchuk, S.; Wachsmann-Hogiu, S. Recent advances in optical label-free characterization of extracellular vesicles. *Nanophotonics* **2022**, *11*, 2827–2863. [CrossRef]

62. Yu, H.; Huang, Y.; Yang, L. Research progress in the use of mesenchymal stem cells and their derived exosomes in the treatment of osteoarthritis. *Ageing Res. Rev.* **2022**, *31*, 101684. [CrossRef]

63. Song, Q.; Yu, H.; Han, J.; Lv, J.; Lv, Q.; Yang, H. Exosomes in urological diseases—Biological functions and clinical applications. *Cancer Lett.* **2022**, *544*, 215809. [CrossRef]

64. Dhar, R.; Mallik, S.; Devi, A. Exosomal microRNAs (exoMIRs): Micromolecules with macro impact in oral cancer. *3 Biotech* **2022**, *12*, 155. [CrossRef] [PubMed]

65. Paskeh, M.D.A.; Entezari, M.; Mirzaei, S.; Zabolian, A.; Saleki, H.; Naghd, M.J.; Sabet, S.; Khoshbakht, M.A.; Hashemi, M.; Hushmandi, K.; et al. Emerging role of exosomes in cancer progression and tumor microenvironment remodeling. *J. Hematol. Oncol.* **2022**, *15*, 83. [CrossRef] [PubMed]
67. Golan-Gerstl, R.; Reif, S. Extracellular vesicles in human milk. Curr. Opin. Clin. Nutr. Metab. Care 2022, 25, 209–215. [CrossRef] [PubMed]

68. Zhang, Z.; Yu, Y.; Zhu, G.; Zeng, L.; Xu, S.; Cheng, H.; Ouyang, Z.; Chen, J.; Pathak, J.L.; Wu, L.; et al. The Emerging Role of Plant-Derived Exosomes-Like Nanoparticles in Immune Regulation and Periodontitis Treatment. Front. Immunol. 2022, 13, 896745. [CrossRef] [PubMed]

69. Wang, Y.; Wang, J.; Ma, J.; Zhou, Y.; Lu, R. Focusing on Future Applications and Current Challenges of Plant Derived Extracellular Vesicles. Pharmaceuticals 2022, 15, 708. [CrossRef]

70. Li, X.; Wang, Q.; Wang, R. Roles of Exosome Genomic DNA in Colorectal Cancer. Front. Pharmacol. 2022, 13, 923232. [CrossRef] [PubMed]

71. Marei, H.E.; Althani, A.; Afifi, N.; Hasan, A.; Caceci, T.; Cifola, L.; Caratelli, S.; Sconocchia, G.; D’Agnano, I.; Cenciarelli, C. Glioma extracellular vesicles for precision medicine: Prognostic and theragnostic application. Discov. Oncol. 2022, 13, 49. [CrossRef] [PubMed]

72. Srinivas, A.N.; Suresh, D.; Kaur, S.; Kumar, D.P. The promise of small particles: Extracellular vesicles as biomarkers in liver pathology. J. Physiol. 2022, in press. [CrossRef]

73. Xia, J.; Miao, Y.; Wang, X.; Huang, X.; Dai, J. Recent progress of dendritic cell-derived exosomes (Dex) as an anti-cancer nanovaccine. Biomed. Pharmacother. 2022, 152, 113250. [CrossRef] [PubMed]

74. Mousavi, S.M.; Amin Mahdian, S.M.; Ebrahimi, M.S.; Taghizadieh, M.; Vosough, M.; Sadri Nahand, J.; Hosseindoost, S.; Vosoughi, 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]

75. Chouaib, B.; Cuisinier, F.; Collart-Dutilleul, P.Y. Dental stem cell-conditioned medium for tissue regeneration: Optimization of production and storage. World J. Stem Cells 2022, 14, 287–302. [CrossRef]

76. Shen, J.; Zhang, M.; Peng, M. Progress of exosome research in systemic lupus erythematosus. Cytokine 2022, 4, 100066. [CrossRef]

77. Liu, H.; Liang, J.; Ye, X.; Huang, M.; Ma, L.; Xie, X.; Liu, D.; Cao, H.; Sima-Gandara, J.; Rengasamy, K.R.R.; et al. The potential role of extracellular vesicles in bioactive compound-based therapy: A review of recent developments. Crit. Rev. Food Sci. Nutr. 2022, in press. [CrossRef] [PubMed]

78. Zhou, X.; Cao, H.; Guo, J.; Yuan, Y.; Ni, G. Effects of BMSC-Derived EVs on Bone Metabolism. Pharmaceuticals 2022, 14, 1012. [CrossRef]

79. Gao, H.; Zhang, L.; Wang, Z.; Yan, K.; Zhao, L.; Xiao, W. Research Progress on Transorgan Regulation of the Cardiovascular and Motor System through Cardiogenic Exosomes. Int. J. Mol. Sci. 2022, 23, 5765. [CrossRef]

80. Lee, C.; Han, J.; Jung, Y. Pathological Contribution of Extracellular Vesicles and Their MicroRNAs to Progression of Chronic Liver Disease. Biology 2022, 11, 637. [CrossRef]

81. Kang, F.; Jiang, F.; Ouyang, L.; Wu, S.; Fu, C.; Liu, Y.; Li, Z.; Tian, Y.; Cao, X.; Wang, X.; et al. Potential Biological Roles of Exosomal Long Non-Coding RNAs in Gastrointestinal Cancer. Front. Cell Dev. Biol. 2022, 10, 886191. [CrossRef] [PubMed]

82. Hart, A.R.; Khan, N.L.A.; Godakumara, K.; Dissanayake, K.; Piibor, J.; Muhandiram, S.; Eapen, S.; Heath, P.R.; Fazeli, A. The role of extracellular vesicles in endometrial receptivity and their potential in reproductive therapeutics and diagnosis. Reprod. Biol. 2022, 22, 100645. [CrossRef] [PubMed]

83. Malekian, F.; Shamsian, A.; Kodam, S.P.; Ullah, M. Exosome engineering for efficient and targeted drug delivery: Current status and future perspective. J. Physiol. 2022, in press. [CrossRef]

84. Fang, Y.; Dai, X. Emerging Roles of Extracellular Non-Coding RNAs in Vascular Diseases. J. Cardiovasc. Transl. Res. 2022, 15, 492–499. [CrossRef]

85. Bazzoni, R.; Tanasi, I.; Turazzi, N.; Krampera, M. Update on the Role and Utility of Extracellular Vesicles in Hematological Malignancies. Stem Cells 2022, 40, 619–629. [CrossRef] [PubMed]

86. Hu, Y.; Sun, Y.; Wan, C.; Dai, X.; Wu, S.; Lo, P.C.; Huang, J.; Lovell, J.F.; Jin, H.; Yang, K. Microparticles: Biogenesis, characteristics and intervention therapy for cancers in preclinical and clinical research. J. Nanobiotechnol. 2022, 20, 189. [CrossRef]

87. Allegra, A.; Petrarca, C.; Di Gioacchino, M.; Casciaro, M.; Musolino, C.; Gangemi, S. Exosome-Mediated Therapeutic Strategies for Management of Solid and Hematological Malignancies. Cells 2022, 11, 1128. [CrossRef]

88. Sykaras, A.G.; Christofidis, K.; Politi, E.; Theocharis, S. Exosomes on Endometrial Cancer: A Biomarkers Treasure Trove? Cancers 2022, 14, 1733. [CrossRef]

89. Huang, Z.; Keramat, S.; Izadirad, M.; Chen, Z.S.; Soukhtanloo, M. The Potential Role of Exosomes in the Treatment of Brain Tumors, Recent Updates and Advances. Front. Oncol. 2022, 12, 869929. [CrossRef]

90. Zhang, P.; Rasheed, M.; Liang, J.; Wang, C.; Feng, L.; Chen, Z. Emerging Potential of Exosomal Non-coding RNA in Parkinson’s Disease: A Review. Front. Aging Neurosci. 2022, 14, 819836. [CrossRef]

91. Liu, K.; Gao, X.; Kang, B.; Liu, Y.; Wang, D.; Wang, Y. The Role of Tumor Stem Cell Exosomes in Cancer Invasion and Metastasis. Front. Oncol. 2022, 12, 836548. [CrossRef]

92. Xu, K.; Jin, Y.; Li, Y.; Huang, Y.; Zhao, R. Recent Progress of Exosome Isolation and Peptide Recognition-Guided Strategies for Exosome Research. Front. Chem. 2022, 10, 844124. [CrossRef] [PubMed]
93. Huldani, H.; Abdalkareem Jasim, S.; Olegovich Bokov, D.; Abdelbasset, W.K.; Nader Shalaby, M.; Thangavelu, L.; Margiana, R.; Qasim, M.T. Application of extracellular vesicles derived from mesenchymal stem cells as potential therapeutic tools in autoimmune and rheumatic diseases. *Int. Immunopharmacol.* **2022**, *106*, 108634. [CrossRef]

94. Letafati, A.; Najafi, S.; Mottahedi, M.; Karimzadeh, M.; Shahini, A.; Garousi, S.; Abbasi-Kolli, M.; Sadri Nahand, J.; Tamehri Zadeh, S.S.; Hamblin, M.R.; et al. MicroRNA let-7 and viral infections: Focus on mechanisms of action. *Cell Mol. Biol. Lett.* **2022**, *27*, 14. [CrossRef]

95. Yang, L.; Patel, K.D.; Rathnam, C.; Thangam, R.; Hou, Y.; Kang, H.; Lee, K.B. Harnessing the Therapeutic Potential of Extracellular Vesicles for Biomedical Applications Using Multifunctional Magnetic Nanomaterials. *Small* **2022**, *18*, e2104783. [CrossRef]

96. Widjaja, G.; Jail, A.T.; Budi, H.S.; Abdelbasset, W.K.; Efendi, S.; Suksatan, W.; Ria, R.S.; Satria, A.P.; Aravindhan, S.; Saleh, M.M.; et al. Mesenchymal stromal/stem cells and their exosomes application in the treatment of intervertebral disc disease: A promising frontier. *Int. Immunopharmacol.* **2022**, *105*, 108537. [CrossRef] [PubMed]

97. Whittle, K.; Kao, S.; Clarke, S.; Grau, G.E.R.; Hosseini-Beheshti, E. Exploring the role of extracellular vesicles and their protein cargo in lung cancer metastasis: A review. *Crit. Rev. Oncol. Hematol.* **2022**, *171*, 103603. [CrossRef]

98. Sharma, S.; Sharma, U. Exosomes in cardiovascular diseases: A blessing or a sin for the mankind. *Mol. Cell Biochem.* **2022**, *477*, 833–847. [CrossRef]

99. Hussain, S.; Fatima, A.; Fan, X.X.; Malik, S.I. REVIEW-The Biological importance of cells secreted Exosomes. *Pak. J. Pharm. Sci.* **2021**, *34*, 2273–2279.

100. 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]

101. Alghamdi, M.; Alamry, S.A.; Bahlas, S.M.; Uversky, V.N.; Redwan, E.M. Circulating extracellular vesicles and rheumatoid arthritis: A proteomic analysis. *Cell Mol. Life Sci.* **2021**, *79*, 25. [CrossRef]

102. Jiang, H.; Zhao, H.; Zhang, M.; He, Y.; Li, X.; Xu, Y.; Liu, X. Hypoxia Induced Changes of Exosome Cargo and Subsequent Biological Effects. *Front. Immunol.* **2022**, *13*, 824188. [CrossRef]

103. Barone, A.; d’Avanzo, N.; Cristiano, M.C.; Paolino, D.; Fresta, M. Macrophage-Derived Extracellular Vesicles: A Promising Tool for Personalized Cancer Therapy. *Biomedicines* **2022**, *10*, 1252. [CrossRef]

104. Suresh, P.S.; Thankachan, S.; Venkatesh, T. Landscape of Clinically Relevant Exosomal tRNA-Derived Non-coding RNAs. *Mol. Biotechnol.* **2022**, in press. [CrossRef]

105. Guo, X.; Sui, R.; Piao, H. Tumor-derived small extracellular vesicles: Potential roles and mechanism in glioma. *J. Nanobiotechnol.* **2022**, *20*, 383. [CrossRef]

106. Yamamoto, T.; Yamamoto, Y.; Ochiya, T. Extracellular vesicle-mediated immunoregulation in cancer. *Int. J. Hematol.* **2022**, in press. [CrossRef]

107. Barone, A.; d’Avanzo, N.; Cristiano, M.C.; Paolino, D.; Fresta, M. Macrophage-Derived Extracellular Vesicles: A Promising Tool for Personalized Cancer Therapy. *Biomedicines* **2022**, *10*, 1252. [CrossRef]

108. Chen, K.; Li, Y.; Xu, L.; Qian, Y.; Liu, N.; Zhou, C.; Liu, J.; Wu, C.; Tang, H. Exosomal Non-Coding RNAs: New Insights into the Biology of Hepatocellular Carcinoma. *Curr. Oncol.* **2022**, *29*, 5383–5406. [CrossRef]

109. Carnino, J.M.; Lee, H. Extracellular vesicles in respiratory disease. *Adv. Clin. Chem.* **2022**, *108*, 105–127. [CrossRef]

110. Kim, S.B. Function and therapeutic development of exosomes for cancer therapy. *Arch. Pharm. Res.* **2022**, *45*, 295–308. [CrossRef]

111. Li, F.; Kang, X.; Xin, W.; Li, X. The Emerging Role of Extracellular Vesicle Derived From Neurons/Neurogliaocytes in Central Nervous System Diseases: Novel Insights into Ischemic Stroke. *Front. Pharmacol.* **2022**, *13*, 890698. [CrossRef]

112. Rother, N.; Yanginlar, C.; Pieterse, E.; Hilbrands, L.; van der Vlag, J. Microparticules in Autoimmunity: Cause or Consequence of Disease? *Front. Immunol.* **2022**, *13*, 822995. [CrossRef]

113. Jing, W.; Wang, H.; Zhan, L.; Yan, W. Extracellular Vesicles, New Players in Sepsis and Acute Respiratory Distress Syndrome. *Front. Cell Infect. Microbiol.* **2022**, *12*, 853840. [CrossRef]

114. Rother, N.; Yanginlar, C.; Pieterse, E.; Hilbrands, L.; van der Vlag, J. Microparticules in Autoimmunity: Cause or Consequence of Disease? *Front. Immunol.* **2022**, *13*, 822995. [CrossRef]

115. Jiang, H.; Zhao, H.; Zhang, M.; He, Y.; Li, X.; Xu, Y.; Liu, X. Hypoxia Induced Changes of Exosome Cargo and Subsequent Biological Effects. *Front. Immunol.* **2022**, *13*, 824188. [CrossRef]

116. Boilard, E.; Bellio, M. Platelet extracellular vesicles and the secretory interactome join forces in health and disease. *Immunol. Rev.* **2022**, in press. [CrossRef]

117. Di Bella, M.A. Overview and Update on Extracellular Vesicles: Considerations on Exosomes and Their Application in Modern Medicine. *Biology* **2022**, *11*, 804. [CrossRef]

118. Quesnel, A.; Broughton, A.; Karagiannis, G.S.; Filippou, P.S. Message in the bottle: Regulation of the tumor microenvironment via exosome-driven proteolyasis. *Cancer Metastasis Rev.* **2022**, in press. [CrossRef]

119. Kumari, M.; Anji, A. Small but Mighty-Exosomes, Novel Intercellular Messengers in Neurodegeneration. *Biology* **2022**, *11*, 413. [CrossRef]

120. Al Halawani, A.; Mathieuex, S.M.; Yeo, G.C.; Hosseini-Beheshti, E.; Weiss, A.S. Extracellular Vesicles: Interplay with the Extracellular Matrix and Modulated Cell Responses. *Int. J. Mol. Sci.* **2022**, *23*, 3389. [CrossRef]
121. Guo, Y.; Zhai, Y.; Wu, L.; Wang, Y.; Wu, P.; Xiong, L. Mesenchymal Stem Cell-Derived Extracellular Vesicles: Pleiotropic Impacts on Breast Cancer Occurrence, Development, and Therapy. *Int. J. Mol. Sci.* **2022**, *23*, 2927. [CrossRef]

122. Gao, Y.; Wang, C.; Jin, F.; Han, G.; Cui, C. Therapeutic effect of extracellular vesicles from different cell sources in traumatic brain injury. *Tissue Cell* **2022**, *76*, 101772. [CrossRef]

123. Keshktar, S.; Kaviani, M.; Soleimanian, S.; Azarpira, N.; Asvarg, Z.; Pakbaz, S. Stem Cell-Derived Exosome as Potential Therapeutics for Microbial Diseases. *Front. Microbiol.* **2022**, *12*, 786111. [CrossRef]

124. Lee, Y.; Kim, J.H. The emerging roles of extracellular vesicles as intercellular messengers in liver physiology and pathology. *Clin. Mol. Hepatol.* **2022**, in press. [CrossRef]

125. Dehkordi, N.R.; Dehkordi, N.R.; Farjoo, M.H. Therapeutic properties of stem cell-derived exosomes in ischemic heart disease. *Eur. J. Pharmacol.* **2022**, *920*, 174839. [CrossRef]

126. Buffolo, F.; Monticone, S.; Camussi, G.; Aiakawa, E. Role of Extracellular Vesicles in the Pathogenesis of Vascular Damage. *Hypertension* **2022**, *79*, 863–873. [CrossRef]

127. Xia, X.; Wang, Y.; Qin, Y.; Zhao, S.; Zheng, J.C. Exosome: A novel neurotransmission modulator or non-canonical neurotransmitter? *Aging Res. Rev.* **2022**, *74*, 101558. [CrossRef]

128. Zhang, W.; Xing, J.; Liu, T.; Zhang, J.; Dai, Z.; Zhang, H.; Wang, D.; Tang, D. Small extracellular vesicles: From mediating cancer cell metastasis to therapeutic value in pancreatic cancer. *Cell Commun. Signal.* **2022**, *20*, 1. [CrossRef]

129. Xing, Y.; Sun, X.; Dou, Y.; Wang, M.; Zhao, Y.; Yang, Q.; Zhao, Y. The Immuno-Modulation Effect of Macrophage-Derived Extracellular Vesicles in Chronic Inflammatory Diseases. *Front. Immunol.* **2021**, *12*, 785728. [CrossRef]

130. Zhu, M.; Li, S.; Li, S.; Wang, H.; Xu, J.; Wang, Y.; Liang, G. Strategies for Engineering Exosomes and Their Applications in Drug Delivery. *J. Biomed. Nanotechnol.* **2021**, *17*, 2271–2297. [CrossRef]

131. Zelli, V.; Compagnoni, C.; Capelli, R.; Corrente, A.; Di Vito Nolfi, M.; Zazzeroni, F.; Alesse, E.; Tessitore, A. Role of exosomal microRNAs in cancer therapy and drug resistance mechanisms: Focus on hepatocellular carcinoma. *Front. Oncol.* **2022**, *12*, 940056. [CrossRef]

132. Canning, P.; Alwan, A.; Khalil, F.; Zhang, Y.; Opara, E.C. Perspectives and Challenges on the Potential Use of Exosomes in Bioartificial Pancreas Engineering. *Ann. Biomed. Eng.* **2022**, in press. [CrossRef]

133. Zheng, C.; Xie, L.; Qin, H.; Liu, X.; Chen, X.; Lv, F.; Wang, L.; Zhu, X.; Xu, J. The Role of Extracellular Vesicles in Systemic Lupus Erythematosus. *Front. Cell Dev. Biol.* **2022**, *10*, 835566. [CrossRef]

134. Wang, J.; Yue, B.L.; Huang, Y.Z.; Lan, X.Y.; Liu, W.J.; Chen, H. Exosomal RNAs: Novel Potential Biomarkers for Diseases-A Review. *Int. J. Mol. Sci.* **2022**, *23*, 2461. [CrossRef]

135. Abreu, C.M.; Costa-Silva, B.; Reis, R.L.; Kundu, S.C.; Caballero, D. Microfluidic platforms for extracellular vesicle isolation, analysis and therapy in cancer. *Lab. Chip* **2022**, *22*, 1093–1125. [CrossRef]

136. Lampropoulou, D.I.; Plakou, E.; Aravantinos, G.; Filippou, D.; Gazouli, M. The Role of Exosomal Non-Coding RNAs in Colorectal Cancer Drug Resistance. *Int. J. Mol. Sci.* **2022**, *13*, 1473. [CrossRef]

137. Moon, B.; Chang, S. Exosome as a Delivery Vehicle for Cancer Therapy. *Cells* **2022**, *11*, 316. [CrossRef]

138. Heo, J.; Kang, H. Exosome-Based Treatment for Atherosclerosis. *Int. J. Mol. Sci.* **2022**, *23*, 10002. [CrossRef]

139. Liu, C.; He, D.; Li, L.; Zhang, S.; Wang, L.; Fan, Z.; Wang, Y. Extracellular vesicles in pancreatic cancer immune escape: Emerging roles and mechanisms. *Pharmacol. Res.* **2022**, *183*, 106364. [CrossRef]

140. 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. *Front. Cell Dev. Biol.* **2022**, *9*, 822149. [CrossRef]

141. Abreu, C.M.; Costa-Silva, B.; Reis, R.L.; Kundu, S.C.; Caballero, D. Microfluidic platforms for extracellular vesicle isolation, analysis and therapy in cancer. *Lab. Chip* **2022**, *22*, 1093–1125. [CrossRef]

142. Lampropoulou, D.I.; Plakou, E.; Aravantinos, G.; Filippou, D.; Gazouli, M. The Role of Exosomal Non-Coding RNAs in Colorectal Cancer Drug Resistance. *Int. J. Mol. Sci.* **2022**, *13*, 1473. [CrossRef]

143. Matsuzaka, Y.; Yashiro, R. Immune Modulation Using Extracellular Vesicles Encapsulated with MicroRNAs as Novel Drug Delivery Systems. *Int. J. Mol. Sci.* **2022**, *23*, 5658. [CrossRef]

144. Wu, R.; Fan, X.; Wang, Y.; Shen, M.; Zheng, Y.; Zhao, S.; Yang, L. Mesenchymal Stem Cell-Derived Extracellular Vesicles in Liver Immunity and Therapy. *Front. Immunol.* **2022**, *13*, 833878. [CrossRef]

145. Parveen, S.; Subramanian, K. Emerging Roles of Extracellular Vesicles in Pneumococcal Infections: Immunomodulators to Potential Novel Vaccine Candidates. *Microbes. Microbiol.* **2022**, *12*, 836070. [CrossRef]

146. Li, W.; Zhang, S.; Wang, D.; Zhang, H.; Shi, Q.; Zhang, Y.; Wang, M.; Ding, Z.; Xu, S.; Gao, B.; et al. Exosomes Immunity Strategy: A Novel Approach for Ameliorating Intervertebral Disc Degeneration. *Front. Cell Dev. Biol.* **2022**, *9*, 822149. [CrossRef]

147. Chen, X.; Chi, H.; Zhao, X.; Fan, R.; Wei, Y.; Han, Y. Role of Exosomes in Immune Microenvironment of Hepatocellular Carcinoma. *J. Oncol.* **2022**, *2022*, 2521025. [CrossRef] [PubMed]

148. Peng, J.; Liang, Q.; Xu, Z.; Cai, Y.; Peng, B.; Li, J.; Zhang, W.; Kang, F.; Hong, Q.; Yan, Y.; et al. Current Understanding of Exosomal MicroRNAs in Glioma Immune Regulation and Therapeutic Responses. *Front. Immunol.* **2022**, *12*, 813747. [CrossRef]

149. 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]
150. Jiang, C.; Fu, Y.; Liu, G.; Shu, B.; Davis, J.; Tofaris, G.K. Multiplexed Profiling of Extracellular Vesicles for Biomarker Development. *Nano-Micro Lett.* **2021**, *14*, 3. [CrossRef] [PubMed]

151. Nicholson, S.; Bacarelli, A.; Prada, D. Role of brain extracellular vesicles in air pollution-related cognitive impairment and neurodegeneration. *Environ. Res.* **2022**, *204*, 112316. [CrossRef]

152. Belkozhayev, A.M.; Al-Yozbaki, M.; George, A.; Ye Niyazova, R.; Sharipov, K.O.; Byrne, L.J.; Wilson, C.M. Extracellular Vesicles, Stem Cells and the Role of miRNAs in Neurodegeneration. *Curr. Neuropsychopharmacol.* **2022**, *20*, 1450–1478. [CrossRef]

153. Picca, A.; Guerra, F.; Calvani, R.; Coelho-Junior, H.J.; Bucci, C.; Marzetti, E. Circulating extracellular vesicles: Friends and foes in neurodegeneration. *Neural. Regen. Res.* **2022**, *17*, 534–542. [CrossRef]

154. Mishra, L.C.; Pandey, U.; Gupta, A.; Gupta, J.; Sharma, M.; Mishra, G. Alternating exosomes and their mimetics as an emergent strategy for targeted cancer therapy. *Front. Mol. Biosci.* **2022**, *9*, 939050. [CrossRef]

155. Baldasici, O.; Pileczki, V.; Cruceriu, D.; Gavrilas, L.I.; Tudoran, O.; Balacescu, L.; Vlase, L.; Balacescu, O. Breast Cancer-Delivered Tumor-associated Exosomes: Release and Potential of Milk Extracellular Vesicles on Colorectal Cancer. *Biomed. Res. Interdiscip. Perspect.* **2022**, *1216–1226*. [CrossRef]

156. Lopatina, T.; Sarcinella, A.; Brizzi, M.F. Tumour Derived Extracellular Vesicles: Challenging Target to Blunt Tumour Immune Evasion. *Cancers* **2022**, *14*, 4020. [CrossRef]

157. Meng, L.; Song, K.; Li, S.; Kang, Y. xosomes: Small Vesicles with Important Roles in the Development, Metastasis and Treatment of Breast Cancer. *Membranes* **2022**, *12*, 775. [CrossRef]

158. Onukwugha, N.E.; Kang, Y.T.; Nagrath, S. Emerging micro-nanotechnologies for extracellular vesicles in immuno-oncology: From target specific isolations to immunomodulation. *Lab. Chip.* **2022**, in press. [CrossRef]

159. Wu, M.; Wang, M.; Jia, H.; Wu, P. Extracellular vesicles: Emerging anti-cancer drugs and advanced functionalization platforms for cancer therapy. *Drug Deliv.* **2022**, *29*, 2513–2538. [CrossRef]

160. Zhao, Y.; Liu, T.; Zhou, M. Immune-Cell-Derived Exosomes for Cancer Therapy. *Mol. Pharm.* **2022**, in press. [CrossRef]

161. Bie, N.; Yong, T.; Wei, Z.; Gan, L.; Yang, X. Extracellular vesicles for improved tumor accumulation and penetration. *Adv. Drug Deliv. Rev.* **2022**, *188*, 114450. [CrossRef]

162. Wang, H.; Yu, L.; Huang, P.; Zhou, Y.; Zheng, W.; Meng, N.; He, R.; Xu, Y.; Keong, T.S.; Cui, Y. Tumor endothelial cell-derived extracellular vesicles contribute to tumor microenvironment remodeling. *Cell. Commun. Signal.* **2022**, *20*, 97. [CrossRef]

163. Babaker, M.A.; Aljoud, F.A.; Alhilaawi, F.; Algarni, A.; Ahmed, A.; Khan, M.I.; Saadeldin, I.M.; Alzahrai, F.A. The Therapeutic Potential of Milk Extracellular Vesicles on Colorectal Cancer. *Int. J. Mol. Sci.* **2022**, *23*, 6812. [CrossRef] [PubMed]

164. Ho, J.; Chaiswing, L.; St Clair, D.K. Extracellular Vesicles and Cancer Therapy: Insights into the Role of Oxidative Stress. *Antioxidants* **2022**, *11*, 1194. [CrossRef]

165. Yu, Z.L.; Liu, J.Y.; Chen, G. Small extracellular vesicle PD-L1 in cancer: The knowns and unknowns. *NPJ Precis. Oncol.* **2022**, *6*, 42. [CrossRef]

166. Glass, S.E.; Coffey, R.J. Recent Advances in the Study of Extracellular Vesicles in Colorectal Cancer. *Gastroenterology,* **2022**, in press. [CrossRef]

167. Chen, H.; Sun, T.; Jiang, C. Extracellular vesicle-based macromolecule delivery systems in cancer immunotherapy. *J. Control. Release* **2022**, *348*, 572–589. [CrossRef] [PubMed]

168. 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]

169. Wang, J.; Wang, X.; Zhang, X.; Shao, T.; Luo, Y.; Wang, W.; Han, Y. Extracellular Vesicles and Hepatocellular Carcinoma: Opportunities and Challenges. *Front. Oncol.* **2022**, *12*, 884369. [CrossRef] [PubMed]

170. Wang, S.E. Extracellular vesicles in cancer therapy. *Semin. Cancer Biol.* **2022**, in press. [CrossRef]
179. Khan, M.I.; Alsayed, R.K.M.E.; Choudhry, H.; Ahmad, A. Exosome-Mediated Response to Cancer Therapy: Modulation of Epigenetic Machinery. *Int. J. Mol. Sci.* 2022, 23, 6222. [CrossRef]

180. Zhang, W.; Hu, X.; Jiang, Z. Small Extracellular Vesicles: Key Forces Mediating the Development and Metastasis of Colorectal Cancer. *Cells* 2022, 11, 1780. [CrossRef]

181. Tuo, B.; Chen, Z.; Dang, Q.; Chen, C.; Zhang, H.; Hu, S.; Sun, Z. Roles of exosomal circRNAs in tumour immunity and cancer progression. *Cell Death Dis.* 2022, 13, 599. [CrossRef]

182. Yang, S.; Wang, J.; Wang, S.; Zhou, A.; Zhao, G.; Li, P. Roles of small extracellular vesicles in the development, diagnosis and possible treatment strategies for hepatocellular carcinoma (Review). *Int. J. Oncol.* 2022, 61, 91. [CrossRef]

183. 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. *Cells* 2022, 11, 1433. [CrossRef]

184. Bai, S.; Wei, Y.; Liu, R.; Xu, R.; Xiang, L.; Du, J. Role of tumour-derived exosomes in metastasis. *Biosens. Bioelectron.* 2022, 114, 112657. [CrossRef] [PubMed]

185. Feng, 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, 13, 795372. [CrossRef] [PubMed]

186. Tian, W.; Lei, N.; Zhou, J.; Chen, M.; Guo, R.; Qin, B.; Li, Y.; Chang, L. Extracellular vesicles in ovarian cancer chemoresistance, metastasis, and immune evasion. *Cell Death Dis.* 2022, 23, 64. [CrossRef] [PubMed]

187. Eguchi, T.; Sheta, M.; Fujii, M.; Calderwood, S.K. Cancer extracellular vesicles, tumoroid models, and tumor microenvironment. *Semin. Cancer Biol.* 2022, in press. [CrossRef]

188. Britschgi, D.; Weber, M.; Wang, J.; Moscat, J. Protective role of extracellular vesicles in a mouse model for acute liver failure. *J. Exp. Med.* 2022, 219, 2477–2490. [CrossRef]

189. Mojtahedin, S.; Nasimi, F.S.; Tajalli, H.; Ebrahimi, S.; Alimohammadzadeh, B.; Rahbarghazi, R.; Mahdipour, M. Light-emitting diode photomodulation of uterine adenocarcinoma cells inhibited angiogenesis capacity via the regulation of exosome biogenesis. *Lasers Med. Sci.* 2022, in press. [CrossRef]

190. Bao, Q.; Huang, Q.; Chen, Y.; Wang, Q.; Sang, R.; Wang, L.; Xie, Y.; Chen, W. Tumor-Derived Extracellular Vesicles Regulate Cancer Progression in the Tumor Microenvironment. *Front. Mol. Biosci.* 2022, 8, 796385. [CrossRef] [PubMed]

191. Tamas, F.; Balasa, R.; Manu, D.; Gyorki, G.; Chinezu, R.; Tamas, C.; Balasa, A. The Importance of Small Extracellular Vesicles in the Cerebral Metastatic Process. *Int. J. Mol. Sci.* 2022, 23, 1449. [CrossRef]

192. Chang, I.C.; Chiu, H.M.; Wu, M.S.; Shen, T.L. The Role of Small Extracellular Vesicles in the Progression of Colorectal Cancer and Its Clinical Applications. *Int. J. Mol. Sci.* 2022, 23, 1379. [CrossRef]

193. Eguchi, T.; Sheta, M.; Fujii, M.; Calderwood, S.K. Cancer extracellular vesicles, tumoroid models, and tumor microenvironment. *Semin. Cancer Biol.* 2022, in press. [CrossRef]

194. Bali, A.; Debnath, A.; Baruah, P.; Das, D.; Jana, K.; Kher, A.; Bhattacharyya, R.; Biswas, S.; Mitra, N.; Chopra, J.; et al. A new role for exosomes in cellular immunity and protection during COVID-19. *Cell Death Dis.* 2022, 13, e12177. [CrossRef] [PubMed]

195. Tuo, B.; Chen, Z.; Dang, Q.; Chen, C.; Zhang, H.; Hu, S.; Sun, Z. Roles of exosomal circRNAs in tumour immunity and cancer progression. *Cell Death Dis.* 2022, 13, 599. [CrossRef]

196. Yang, S.; Wang, J.; Wang, S.; Zhou, A.; Zhao, G.; Li, P. Roles of small extracellular vesicles in the development, diagnosis and possible treatment strategies for hepatocellular carcinoma (Review). *Int. J. Oncol.* 2022, 61, 91. [CrossRef]

197. Nan, W.; Zhang, C.; Wang, H.; Chen, H.; Ji, S. Direct Modification of Extracellular Vesicles and Its Applications for Cancer Therapy: A Mini-Review. *Front. Chem.* 2022, 10, 910341. [CrossRef]

198. Chand, S.; Gowen, A.; Savine, M.; Moore, D.; Clark, A.; Huynh, W.; Wu, N.; Odegaard, K.; Weyrich, L.; Bevins, R.A.; et al. A comprehensive study to delineate the role of an extracellular vesicle-associated microRNA-29a in chronic methamphetamine use disorder. *J. Exercell. Vesicles* 2021, 10, e12177. [CrossRef]

199. Zhang, Q.; Jeppesen, D.K.; Higginbotham, J.N.; Graves-Deal, R.; Trinh, V.Q.; Ramirez, M.A.; Sohn, Y.; Neininger, A.C.; Taneja, N.; McKinley, E.T.; et al. Supermeres are functional extracellular nanoparticles replete with disease biomarkers and therapeutic targets. *Nat. Cell Biol.* 2021, 23, 1240–1254. [CrossRef]

200. Hsiao, Y.P.; Chen, C.; Lee, C.M.; Chen, P.Y.; Chung, W.H.; Wang, Y.P.; Hung, Y.C.; Cheng, C.M.; Chen, C.; Ko, B.H.; et al. Differences in the Quantity and Composition of Extracellular Vesicles in the Aqueous Humor of Patients with Retinal Neovascular Diseases. *Diagnostics* 2021, 11, 1276. [CrossRef]
205. Anand, S.; Samuel, M.; Mathivanan, S. Exomeres: A New Member of Extracellular Vesicles Family. Subcell. Biochem. 2021, 97, 89-97. [CrossRef]

206. Zhang, Q.; Higginbotham, J.N.; Jeppesen, D.K.; Yang, Y.P.; Li, W.; McKinley, E.T.; Graves-Deal, R.; Ping, J.; Britain, C.M.; Dorsett, K.A.; et al. Transfer of Functional Cargo in Exomeres. Cell Rep. 2019, 27, 940-954.e6. [CrossRef]

207. Zhang, H.; Freitas, D.; Kim, H.S.; Fabijanic, K.; Li, Z.; Chen, H.; Mark, M.T.; Molina, H.; Martin, A.B.; Bojmar, L.; et al. Identification of distinct nanoparticles and subsets of extracellular vesicles by asymmetric flow field-flow fractionation. Nat. Cell Biol. 2018, 20, 332-343. [CrossRef]

208. Zaldivia, M.T.K.; McFadyen, J.D.; Lim, B.; Wang, X.; Peter, K. Platelet-Derived Microvesicles in Cardiovascular Diseases. Front. Cardiovasc. Med. 2017, 4, 74. [CrossRef]

209. Ståhl, A.L.; Johansson, K.; Mossberg, M.; Kahn, R.; Karpman, D. Exosomes and microvesicles in normal physiology, pathophysiology, and renal diseases. Pediatr. Nephrol. 2019, 34, 11-30. [CrossRef]

210. Zhang, W.; Huang, F.; Lin, J.; Zeng, H. The Role of Extracellular Vesicles in Osteoporosis: A Scoping Review. Membranes 2022, 12, 324. [CrossRef] [PubMed]

211. Yang, Z.; She, D.; Sun, C.; Gong, M.; Rong, Y. Dumbbell structure probe-triggered rolling circle amplification (RCA)-based detection scaffold for sensitive and specific neonatal infection-related small extracellular vesicle (sEV) detection. Anal. Methods 2022, 14, 1534-1539. [CrossRef]

212. Gamperl, H.; Plattfaut, C.; Freund, A.; Quecke, T.; Theophil, F.; Gieseler, F. Extracellular vesicles from malignant effusions induce tumor cell migration: Inhibitory effect of LMWH tinzaparin. Cell Biol. Int. 2016, 40, 1050-1061. [CrossRef]

213. Asea, A.; Jean-Pierre, C.; Kaur, P.; Rao, P.; Linhares, I.M.; Skupski, D.; Witkin, S.S. Heat shock protein-containing exosomes in mid-trimester amniotic fluids. J. Reprod. Immunol. 2008, 79, 12-17. [CrossRef] [PubMed]

214. Calvo, V.; Izquierdo, M. Inducible Polarized Secretion of Exosomes in T and B Lymphocytes. Int. J. Mol. Sci. 2020, 21, 2631. [CrossRef] [PubMed]

215. Ye, J.; Liu, X. Macrophase-Derived Small Extracellular Vesicles in Multiple Diseases: Biogenesis, Function, and Therapeutic Applications. Front. Cell Dev. Biol. 2020, 10, 913110. [CrossRef] [PubMed]

216. Zhang, X.; Xu, D.; Song, Y.; He, R.; Wang, T. Research Progress in the Application of Exosomes in Immunotherapy. Front. Immunol. 2022, 13, 731516. [CrossRef] [PubMed]

217. 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]

218. Skogberg, G.; Telemo, E.; Ekwall, O. Exosomes in the Thymus: Antigen Transfer and Vesicles. Front. Immunol. 2015, 6, 366. [CrossRef] [PubMed]

219. Martínez-Ustarorde, A.; De Palma, M. Dendritic cell cross-dressing and tumor immunity. EMBO Mol. Med. 2022, 12, e16523. [CrossRef]

220. Mo, L.H.; Han, H.Y.; Jin, Q.R.; Song, Y.N.; Wu, G.H.; Zhang, Y.; Yang, L.T.; Liu, T.; Liu, Z.G.; Feng, Y.; et al. T cell activator-carrying extracellular vesicles induce antigen-specific regulatory T cells. Clin. Exp. Immunol. 2021, 206, 129-140. [CrossRef]

221. 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]

222. Han, J.M.; Song, H.Y.; Lim, S.T.; Kim, K.I.; Seo, H.S.; Byun, E.B. Immunostimulatory Potential of Extracellular Vesicles Isolated from an Edible Plant, Petasites japonicus, via the Induction of Murine Dendritic Cell Maturation. Int. J. Mol. Sci. 2021, 22, 10634. [CrossRef]

223. Yang, Y.; Huang, H.; Li, Y. Roles of exosomes and exosome-derived miRNAs in pulmonary fibrosis. Front. Pharmacol. 2022, 13, 928933. [CrossRef]

224. Zou, J.; Peng, H.; Liu, Y. The Roles of Exosomes in Immunoregulation and Autoimmune Thyroid Diseases. Front. Immunol. 2021, 12, 757674. [CrossRef]

225. Fu, C.; Peng, P.; Loschko, J.; Feng, L.; Pham, P.; Cui, W.; Lee, K.P.; Krug, A.B.; Jiang, A. Plasmacytoid dendritic cells cross-prime naive CD8 T cells by transferring antigen to conventional dendritic cells through exosomes. Proc. Natl. Acad. Sci. USA 2020, 117, 23730-23741. [CrossRef]

226. Pfister, H. Neutrophil Extracellular Traps and Neutrophil-Derived Extracellular Vesicles: Common Players in Neutrophil Effector Functions. Diagnostics 2022, 12, 1715. [CrossRef] [PubMed]

227. Ou, Q.; Dou, X.; Tang, J.; Wu, P.; Pan, D. Small extracellular vesicles derived from PD-L1-modified mesenchymal stem cell promote Tregs differentiation and prolong allograft survival. Cell Tissue Res. 2022, in press. [CrossRef] [PubMed]

228. Santos, P.; Almeida, F. Exosome-Based Vaccines: History, Current State, and Clinical Trials. Front. Immunol. 2021, 12, 711565. [CrossRef]

229. Fernández-Delgado, I.; Calzada-Fraile, D.; Sánchez-Madrid, F. Immune Regulation by Dendritic Cell Extracellular Vesicles in Cancer Immunotherapy and Vaccines. Cancers 2020, 12, 3558. [CrossRef]

230. Nikfarjam, S.; Rezaie, J.; Kashanchi, F.; Jafari, R. Dexosomes as a cell-free vaccine for cancer immunotherapy. J. Exp. Clin. Cancer Res. 2020, 39, 258. [CrossRef] [PubMed]

231. Sabanovic, B.; Piva, F.; Cecati, M.; Giuliani, M. Promising Extracellular Vesicle-Based Vaccines against Viruses, Including SARS-CoV-2. Biology 2021, 10, 94. [CrossRef]
Vaccines 2022, 10, 1691

232. Teshima, T.; Yuchi, Y.; Suzuki, R.; Matsumoto, H.; Koyama, H. Immunomodulatory Effects of Canine Adipose Tissue Mesenchymal Stem Cell-Derived Extracellular Vesicles on Stimulated CD4+ T Cells Isolated from Peripheral Blood Mononuclear Cells. *J. Immunol. Res.* 2021, 2021, 2993043. [CrossRef]

233. Zhang, J.; Li, P.; Zhao, G.; He, S.; Xu, D.; Jiang, W.; Peng, Q.; Li, Z.; Xie, Z.; Zhang, H.; et al. Mesenchymal stem cell-derived extracellular vesicles protect retina in a mouse model of retinitis pigmentosa by anti-inflammation through miR-146a-Nr4a3 axis. *Stem Cell Res. Ther.* 2022, 13, 394. [CrossRef]

234. Wang, C.; Börgér, V.; Mohamud Yusuf, A.; Tertel, T.; Stamboulï, O.; Murke, F.; Freund, N.; Kleinschnitz, C.; Herz, J.; Gunzer, M.; et al. Postsclerotic Neuroprotection Associated With Anti-Inflammatory Effects by Mesenchymal Stromal Cell-Derived Small Extracellular Vesicles in Aged Mice. *Stroke* 2022, 53, e14–e18. [CrossRef]

235. Ha, D.H.; Kim, H.K.; Lee, J.; Kwon, H.H.; Park, G.H.; Yang, S.H.; Jung, J.Y.; Choi, H.; Lee, J.H.; Sung, S.; et al. Mesenchymal Stem/Stromal Cell-Derived Exosomes for Immunomodulatory Therapeutics and Skin Regeneration. *Cells* 2020, 9, 1157. [CrossRef]

236. Lu, T.; Zhang, Z.; Zhang, J.; Pan, X.; Zhu, X.; Wang, X.; Li, Z.; Ruan, M.; Li, H.; Chen, W.; et al. CD73 in small extracellular vesicles derived from HNSCC defines tumour-associated immunosuppression mediated by macrophages in the microenvironment. *J. Extracell. Vesicles* 2022, 11, e12218. [CrossRef] [PubMed]

237. Buzas, E.I. The roles of extracellular vesicles in the immune system. *Nat. Rev. Immunol.* 2022, in press. [CrossRef]

238. Fu, C.; Ma, T.; Zhou, L.; Mi, Q.S.; Jiang, A. Dendritic Cell-Based Vaccines Against Cancer: Challenges, Advances and Future Opportunities. *Immunol. Invest.* 2022, 10, 1–26. [CrossRef]

239. Chi, H.; Hao, Y.; Wang, X.; Tang, L.; Deng, Y.; Chen, X.; Gao, F.; Sha, O.; Jin, G. A Therapeutic Whole-Tumor-Cell Vaccine Covalently Conjugated with a TLR7 Agonist. *Cells* 2011, 11, 1866. [CrossRef]

240. Dhandapani, H.; Jayakumar, H.; Seetharaman, A.; Singh, S.S.; Ganeshrajah, S.; Jagadish, N.; Suri, A.; Thangarajan, R.; Ramanathan, P. Dendritic cells matured with recombinant human sperm associated antigen 9 (rhSPA9) induce CD4+, CD8+ T cells and activate NK cells. A potential candidate molecule for immunotherapy in cervical cancer. *Cancer Cell Int.* 2021, 21, 473. [CrossRef] [PubMed]

241. He, Z.; Jia, H.; Zheng, M.; Wang, H.; Yang, W.; Gao, L.; Zhang, Z.; Xue, J.; Xu, B.; Yang, W.; et al. Trp2 Peptide-Assembled Nanoparticles with Intrinsically Self-Chelating β3Cu Properties for PET Imaging Tracking and Dendritic Cell-Based Immunotherapy against Melanoma. *ACS Appl. Bio. Mater.* 2021, 4, 5707–5716. [CrossRef] [PubMed]

242. Kanda, Y.; Okazaki, T.; Kataki, T. Motility Dynamics of T Cells in Tumor-Draining Lymph Nodes: A Rational Indicator of Antitumor Response and Immune Checkpoint Blockade. *Cancers* 2021, 13, 4616. [CrossRef]

243. Kotsias, F.; Cebrian, I.; Alloatti, A. Antigen processing and presentation. *Int. Rev. Cell Mol. Biol.* 2021, 364, 1–69. [CrossRef]

244. Dhandapani, H.; Jayakumar, H.; Seetharaman, A.; Singh, S.S.; Ganeshrajah, S.; Jagadish, N.; Suri, A.; Thangarajan, R.; Ramanathan, P. Dendritic cells matured with recombinant human sperm associated antigen 9 (rhSPA9) induce CD4+, CD8+ T cells and activate NK cells. A potential candidate molecule for immunotherapy in cervical cancer. *Cancer Cell Int.* 2021, 21, 473. [CrossRef] [PubMed]

245. Rolig, A.S.; Rose, D.C.; McGee, G.H.; Rubas, W.; Kivimäe, S.; Redmond, W.L. Combining bempegaldesleukin (CD122-preferential IL-2 pathway agonist) and NKTR-262 (TLR7/8 agonist) improves systemic antitumor CD8+ T cell cytotoxicity over BEMPEG+RT. *J. Immunother. Cancer* 2020, 8, e004218. [CrossRef]

246. Marashi, H.; Belighi, M.; Chaboksavar, M.; Khaksar, S.; Tehrani, H.; Abiri, A. In silico analysis and in planta production of recombinant ccl21/IL1β protein and characterization of its in vitro anti-tumor and immunogenic activity. *PLoS ONE* 2022, 17, e026101. [CrossRef] [PubMed]

247. Millán-Salanova, M.; Vicente-Manzanares, M. The interface between biochemical signaling and cell mechanics shapes T lymphocyte migration and activation. *Eur. J. Cell Biol.* 2022, 101, 151236. [CrossRef] [PubMed]

248. Baljon, J.J.; Wilson, J.T. Bioinspired vaccines to enhance MHC class-I antigen cross-presentation. *Curr. Opin. Immunol.* 2022, 77, 102215. [CrossRef] [PubMed]

249. Jongsma, M.L.M.; Neefjes, J.; Spaapen, R.M. Playing hide and seek: Tumor cells in control of MHC class I antigen presentation. *Mol. Immunol.* 2021, 136, 36–44. [CrossRef]

250. Weishaupt, C.; Steinert, M.; Brunner, G.; Schulze, H.J.; Fühlbrigge, R.C.; Goerke, T.; Loser, K. Activation of human vascular endothelium in melanoma metastases induces ICAM-1 and E-selectin expression and results in increased infiltration with effector lymphocytes. *Exp. Dermatol.* 2019, 28, 1258–1269. [CrossRef]

251. Li, S.J.; Chen, J.X.; Sun, Z.J. Improving antitumor immunity using antiangiogenic agents: Mechanistic insights, current progress, and clinical challenges. *Cancer Commun.* 2021, 41, 830–850. [CrossRef]

252. Zhou, X.; Li, C.; Zhang, Z.; Li, D.Y.; Du, J.; Ding, P.; Meng, H.; Xu, H.; Li, R.; Ho, E.; et al. Kinetics of plasma cfDNA predicts clinical response in non-small cell lung cancer patients. *Sci. Rep.* 2021, 11, 7633. [CrossRef]

253. Bauer, S.M.; Williams, M.A.; Howell, A.P.; Schwarz, E.; Smith, E.S.; Zauderer, M. Maximizing immune responses: The effects of covalent peptide linkage to beta-2-microglobulin. *Oncol. Res.* 2008, 17, 20–216. [CrossRef]

254. Chang, C.C.; Ogino, T.; Mullins, D.W.; Oliver, J.L.; Yamshchikov, G.V.; Bandoh, N.; Slungluff, C.L., Jr.; Ferrone, S. Defective human leukocyte antigen class I-associated antigen presentation caused by a novel beta2-microglobulin loss-of-function in melanoma cells. *J. Biol. Chem.* 2006, 281, 18763–18773. [CrossRef]

255. Guerreiro-Cacais, A.O.; Uzunel, M.; Levitskaya, J.; Levitsky, V. Inhibition of heavy chain and beta2-microglobulin synthesis as a mechanism of major histocompatibility complex class I downregulation during Epstein-Barr virus replication. *J. Virol.* 2007, 81, 1390–1400. [CrossRef]
256. Li, X.; Xiang, Y.; Li, F.; Yin, C.; Li, B.; Ke, X. WNT/β-Catenin Signaling Pathway Regulating T Cell-Inflammation in the Tumor Microenvironment. *Front. Immunol.* 2019, 10, 2293. [CrossRef]

257. Gerhard, G.M.; Bill, R.; Messemaker, M.; Klein, A.M.; Pittet, M.J. Tumor-infiltrating dendritic cell states are conserved across solid human cancers. *J. Exp. Med.* 2021, 218, e20200264. [CrossRef]

258. Saito, Y.; Komori, S.; Kotani, T.; Murata, Y.; Matozaki, T. The Role of Type-2 Conventional Dendritic Cells in the Regulation of Tumor Immunity. *Cancers* 2022, 14, 1976. [CrossRef]

259. Kobayashi, T.; Oishi, K.; Okamura, A.; Maeda, S.; Komuro, A.; Hamaguchi, Y.; Fujimoto, M.; Takehara, K.; Matsushita, T. Regulatory B1a Cells Suppress Melanoma Tumor Immunity via IL-10 Production and Inhibiting T Helper Type 1 Cytokine Production in Tumor-Infiltrating CD8+ T Cells. *J. Investig. Dermatol.* 2019, 139, 1535–1544.e1. [CrossRef]

260. Bellmann, L.; Cappellano, G.; Schachtl-Riess, J.F.; Prokopi, A.; Seretis, A.; Ortner, D.; Tripp, C.H.; Brinckerhoff, C.E.; Mullins, D.W.; Stoitzenz, P. A TLR7 agonist strengthens T and NK cell function during BRAF-targeted therapy in a preclinical melanoma model. *Int. J. Cancer* 2020, 146, 1394–1420. [PubMed]

261. Xiao, Y.; Zhang, L.; Zhu, J.; Zhang, Y.; Yang, R.; Yan, J.; Huang, R.; Zheng, C.; Xiao, W.; Huang, C.; et al. Predicting the herbal medicine triggering innate anti-tumor immunity from a system pharmacology perspective. *Biomed. Pharmacother.* 2021, 143, 112105. [CrossRef]

262. Artinger, M.; Gerken, O.J.; Purvanov, V.; Legler, D.F. Distinct Fates of Chemokine and Surrogate Molecule Gradients: Consequences for CCR7-Guided Dendritic Cell Migration. *Front. Immunol.* 2019, 10, 2268. [CrossRef]

263. Anderko, R.R.; Rinaldo, C.R.; Mailliard, R.B. IL-18 Responsiveness Defines Limitations in Immune Help for Specialized FcRγ− Natural Killer Cells and Enhances IL-18-Driven Dendritic Cells Activation. *Front. Immunol.* 2019, 10, 2265–2278. [CrossRef]

264. Lau, C.M.; Tiniakou, I.; Perez, O.A.; Kirkling, M.E.; Yap, G.S.; Hock, H.; Reizis, B. Transcription factor Etv6 regulates functional differentiation of cross-presenting classical dendritic cells. *J. Exp. Med.* 2018, 215, 2265–2278. [CrossRef]

265. Nizza, S.T.; Campbell, J.J. CD11b+ migratory dendritic cells mediate CD8 T cell cross-priming and cutaneous imprinting after topical immunization. *Plos ONE* 2014, 9, e91054. [CrossRef]

266. Bergamaschi, C.; Pandit, H.; Nagy, B.A.; Stellas, D.; Jensen, S.M.; Bear, J.; Cam, M.; Valentin, A.; Fox, B.A.; Felber, B.K.; et al. Heterodimeric IL-15 delays tumor growth and promotes intratumoral CTL and dendritic cell accumulation by a cytokine network involving XCL1, IFN-γ, CXCL9 and CXCL10. *J. Immunother. Cancer* 2020, 8, e000999. [CrossRef]

267. Böttcher, J.P.; Bonavita, E.; Chakravarty, P.; Blees, H.; Cabeza-Cabrerizo, M.; Sammicheli, S.; Rogers, N.C.; Sahai, E.; Zelenay, S.; et al. The atypical chemokine receptor CCRL1 shapes functional CCL21 gradients in lymph nodes. *Nat. Immunol.* 2014, 15, 623–630. [CrossRef]
280. Pouliot, C.C.; Noor, S.; Crane, J.; Masek, K.; Carter, W.; Lo, D.D.; Wilson, E.H.; Carson, M.J. CNS-derived CCL21 is both sufficient to drive homeostatic CD4+ T cell proliferation and necessary for efficient CD4+ T cell migration into the CNS parenchyma following Toxoplasma gondii infection. *Brain Behav. Immun.* 2011, 25, 883–896. [CrossRef]

281. Jiang, K.; Zhang, Q.; Fan, Y.; Li, J.; Zhang, J.; Wang, W.; Fan, J.; Guo, Y.; Liu, S.; Hao, D.; et al. MYC inhibition reprograms tumor immune microenvironment by recruiting T lymphocytes and activating the CD40/CD40L system in osteosarcoma. *Cell Death Discov.* 2022, 8, 117. [CrossRef] [PubMed]

282. Müerköster, S.; Laman, J.D.; Rocha, M.; Umansky, V.; Schirrmacher, V. Functional and in situ evidence for nitric oxide production driven by CD40-CD40L interactions in graft-versus-leukemia-reactivity. *Clin. Cancer Res.* 2000, 6, 1988–1996. [PubMed]

283. Zhang, X.; Zheng, F.; Prestwood, T.R.; Zhang, H.; Carmi, Y.; Tolentino, L.L.; Wu, N.; Choi, O.; Winer, D.A.; Strober, S.; et al. Human Regulatory Dendritic Cells Develop From Monocytes in Response to Signals From Regulatory and Helper T Cells. *Front. Immunol.* 2020, 11, 982. [CrossRef] [PubMed]

284. Heidegger, S.; Kreppel, D.; Bseider, M.; Stritzke, F.; Nedelko, T.; Wintges, A.; Bek, S.; Fischer, J.C.; Graalmann, T.; Kalinke, U.; et al. RIG-I activating immunostimulatory RNA boosts the efficacy of anticancer vaccines and synergizes with immune checkpoint blockade. *EBioMedicine* 2019, 41, 146–155. [CrossRef]

285. Dou, X.; Hua, Y.; Chen, Z.; Chao, F.; Li, M. Extracellular vesicles containing PD-L1 contribute to CD8+ T-cell immune suppression and predict poor outcomes in small cell lung cancer. *Clin. Exp. Immunol.* 2022, 207, 307–317. [CrossRef]

286. Xu, M.; Zhou, C.; Wang, Y.; Cao, J.; Yang, X.; Qin, L.; Liu, R.; Zhou, Y.; Tong, F.; Umeshappa, C.S.; et al. Phagocyte-membrane-coated and laser-responsive nanoparticles control primary and metastatic cancer by inducing anti-tumor immunity. *Biomaterials* 2020, 255, 120159. [CrossRef] [PubMed]

287. Shah, K.; Mallik, S.B.; Gupta, P.; Iyer, A. Targeting Tumour-Associated Fibroblasts in Cancers. *Front. Oncol.* 2022, 12, 908156. [CrossRef]

288. Ghahremanifard, P.; Chanda, A.; Bonni, S.; Bose, P. TGF-β Mediated Immune Evasion in Cancer-Spotlight on Cancer-Associated Fibroblasts. *Cancers* 2020, 12, 3650. [CrossRef]

289. Affo, S.; Yu, L.X.; Schwabe, R.F. The Role of Cancer-Associated Fibroblasts and Fibrosis in Liver Cancer. *Annu. Rev. Pathol.* 2017, 12, 153–186. [CrossRef]

290. Gao, X.; Hua, Y.; Chen, Z.; Li, M. Extracellular vesicles containing PD-L1 contribute to CD8+ T-cell immune suppression and predict poor outcomes in small cell lung cancer. *Clin. Exp. Immunol.* 2022, 207, 307–317. [CrossRef]

291. Xu, M.; Zhou, C.; Weng, J.; Chen, Z.; Zhou, Q.; Gao, J.; Shi, G.; Ke, A.; Ren, N.; Sun, H.; et al. Tumor associated macrophages-derived exosomes facilitate hepatoctelial carcinoma malignance by transferring IncMMPA to tumor cells and activating glycolysis pathway. *J. Exp. Clin. Cancer Res.* 2022, 41, 253. [CrossRef]

292. Wang, M.; Cai, W.; Yang, A.J.; Wang, C.Y.; Zhang, C.L.; Liu, W.; Xie, X.F.; Gong, Y.Y.; Zhao, Y.Y.; Wu, W.C.; et al. Gastric cancer cell-derived extracellular vesicles disrupt endothelial integrity and promote metastasis. *Cancer Lett.* 2022, 545, 215827. [CrossRef] [PubMed]

293. Wu, J.; Li, S.; Zhang, P. Tumor-derived exosomes: Immune properties and clinical application in lung cancer. *Cancer Drug Resist.* 2022, 5, 102–113. [CrossRef] [PubMed]

294. Sadeghi Najafabadi, S.A.; Bolhassani, A.; Aghasadeghi, M.R. Tumor cell-based vaccine: An effective strategy for eradication of cancer cells. *Immunotherapy* 2022, 14, 639–654. [CrossRef] [PubMed]

295. Jahan, S.; Mukherjee, S.; Ali, S.; Bhardwaj, U.; Choudhary, R.K.; Balakrishnan, S.; Naseem, A.; Mir, S.A.; Banawas, S.; Alaiadareous, M.; et al. Pioneer Role of Extracellular Vesicles as Modulators of Cancer Initiation in Progression, Drug Therapy, and Vaccine Prospects. *Cells* 2022, 11, 490. [CrossRef] [PubMed]

296. Thakur, A.; Parra, D.C.; Motebbejead, P.; Brocchi, M.; Chen, H.J. Exosomes: Small vesicles with big roles in cancer, vaccine development, and therapeutics. *Bioact. Mater.* 2021, 10, 281–294. [CrossRef]

297. Guo, W.; Qiao, T.; Dong, B.; Li, T.; Liu, Q.; Xu, X. The Effect of Hypoxia-Induced Exosomes on Anti-Tumor Immunity and Its Implication for Immunotherapy. *Front. Immunol.* 2022, 13, 915985. [CrossRef] [PubMed]

298. 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, 3135. [CrossRef]

299. Whiteside, T.L. The Role of Tumor-Derived Exosomes (TEX) in Shaping Anti-Tumor Immune Competence. *Cells* 2021, 10, 3054. [CrossRef]

300. Kowal, J.; Tkach, M. Dendritic cell extracellular vesicles. *Int. Rev. Cell Mol. Biol.* 2019, 349, 213–249. [CrossRef]

301. Zeng, F.; Morelli, A.E. Extracellular vesicle-mediated MHC cross-dressing in immune homeostasis, transplantation, infectious diseases, and cancer. *Semin. Immunopathol.* 2018, 40, 477–490. [CrossRef]

302. Hodge, A.L.; Baxter, A.A.; Poon, I.K.H. Gift bags from the sentinel cells of the immune system: The diverse role of dendritic cell-derived extracellular vesicles. *J. Leukoc. Biol.* 2022, 111, 903–920. [CrossRef]

303. Quaglia, M.; Dellepiane, S.; Guglielmetti, G.; Merlotti, G.; Castellano, G.; Cantaluppi, V. Extracellular Vesicles as Mediators of Cellular Crosstalk Between Immune System and Kidney Graft. *Front. Immunol.* 2020, 11, 74. [CrossRef]

304. Lindenbergh, M.F.S.; Stoorvogel, W. Antigen Presentation by Extracellular Vesicles from Professional Antigen-Presenting Cells. *Front. Immunol.* 2018, 36, 435–459. [CrossRef]

305. Morishita, M.; Takahashi, Y.; Nishikawa, M.; Arizumi, R.; Takakura, Y. Enhanced Class I Tumor Antigen Presentation via Cytosolic Delivery of Exosomal Cargos by Tumor-Cell-Derived Exosomes Displaying a pH-Sensitive Fusogenic Peptide. *Mol. Pharm.* 2017, 14, 4079–4086. [CrossRef]
305. Arima, Y.; Liu, W.; Takahashi, Y.; Nishikawa, M.; Takakura, Y. Effects of Localization of Antigen Proteins in Antigen-Loaded Exosomes on Efficiency of Antigen Presentation. *Mol. Pharm.* 2019, 16, 2509–2514. [CrossRef] [PubMed]

306. Morishita, M.; Takahashi, Y.; Matsumoto, A.; Nishikawa, M.; Takakura, Y. Exosome-based tumor antigens-adjuvant co-delivery utilizing genetically engineered tumor cell-derived exosomes with immunostimulatory CpG DNA. *Biomaterials* 2016, 111, 55–65. [CrossRef]

307. Liu, W.; Takahashi, Y.; Morishita, M.; Nishikawa, M.; Takakura, Y. Development of CD40L-modified tumor small extracellular vesicles for effective induction of antitumor immune response. *Nanomedicine* 2020, 15, 1641–1652. [CrossRef]

308. Amadio, G.; Cichy, J.; Conde, P.; Matteoli, G.; Moreau, A.; Ochando, J.; Oral, B.H.; Pekarova, M.; Ryan, E.J.; Roth, J.; et al. Role of myeloid regulatory cells (MRCs) in maintaining tissue homeostasis and promoting tolerance in autoimmunity, inflammatory disease and transplantation. *Cancer Immunol. Immunother.* 2019, 68, 661–672. [CrossRef] [PubMed]

309. Soltani, S.; Mahmoudi, M.; Farhadi, E. Dendritic Cells Currently under the Spotlight; Classification and Subset Based upon New Markers. *Immunol. Invest.* 2021, 50, 646–661. [CrossRef] [PubMed]

310. Morishita, M.; Takahashi, Y.; Nishikawa, M.; Sano, K.; Kato, K.; Yamashita, T.; Imai, T.; Saji, H.; Takakura, Y. Quantitative analysis of tissue distribution of the B16BL6-derived exosomes using a streptavidin-lactadherin fusion protein and iodine-125-labeled biotin derivative after intravenous injection in mice. *J. Pharm. Sci.* 2015, 104, 705–713. [CrossRef]

311. Peng, Y.; Bai, W.; Wang, Z.; Yu, H. TLR9/NF-κB Pathway Regulates Brucella CpG DNA-mediated Cytokine Response in Human Peripheral Blood Mononuclear Cells. *Iran. J. Immunol.* 2021, 18, 268–278. [CrossRef]

312. Tang, Y.; Ma, D.; Ming, S.; Zhang, L.; Zhou, J.; Shan, G.; Chen, Z.; Lu, X.; Zuo, D. Mannan-binding lectin reduces CpG DNA-induced inflammatory cytokine production by human monocytes. *Microbiol. Immunol.* 2015, 59, 231–237. [CrossRef]

313. He, W.; Yu, Q.; Zhou, Z.; Wang, P. CpG oligonucleotides induce an immune response of odontoblasts through the TLR9, MyD88 and NF-kappaB pathways. *Biochem. Biophys. Res. Commun.* 2010, 399, 274–278. [CrossRef] [PubMed]

314. Kim, D.; Kim, T.H.; Wu, G.; Park, B.K.; Ha, J.H.; Kim, Y.S.; Lee, K.; Lee, Y.; Kwon, H.J. Extracellular Release of CD11b by TLR9 Stimulation in Macrophages. *PLoS ONE* 2016, 11, e0150677. [CrossRef]

315. Kitai, Y.; Kawasaki, T.; Sueyoshi, T.; Kobiyama, K.; Ishii, K.; Jou, Z.; Akira, S.; Matsuda, T.; Kawai, T. DNA-Containing Exosomes Derived from Cancer Cells Treated with Topotecan Activate a STING-Dependent Pathway and Reinforce Antitumor Immunity. *J. Immunol.* 2017, 198, 1649–1659. [CrossRef] [PubMed]

316. Hazzari, A.; Soudi, S.; Malekpour, K.; Mahmoudi, M.; Rahimi, A.; Hashemi, S.M.; Varma, R.S. Immune cells-derived exosomes function as a double-edged sword: Role in disease progression and their therapeutic applications. *BioMark. Res.* 2022, 10, 30. [CrossRef] [PubMed]

317. Lindenbergh, M.F.S.; Wubbolts, R.; Borg, E.G.F.; van’t Veld, E.M.; Boes, M.; Stoorvogel, W. Dendritic cells release exosomes together with phagocytosed pathogen; potential implications for the role of exosomes in antigen presentation. *J. Extracell. Vesicles* 2020, 9, 1798606. [CrossRef]

318. Deng, C.J.; Liu, L.; Liu, L.Z.; Wang, Q.Q.; Guo, X.L.; Lee, W.H.; Li, S.A.; Zhang, Y. A secreted pore-forming protein modulates cellular endolysosomes to augment antigen presentation. *FASEB J.* 2020, 34, 13609–13625. [CrossRef]

319. Hao, S.; Liu, Y.; Yuan, J.; Zhang, X.; He, T.; Wu, X.; Wei, Y.; Sun, D.; Xiang, J. Novel exosome-targeted CD4+ T cell vaccine counteracting CD4+25+ regulatory T cell-mediated immune suppression and stimulating efficient central memory CD8+ CTL responses. *J. Immunol.* 2007, 179, 2731–2740. [CrossRef]

320. Utsugi-Kobukai, S.; Fujimaki, H.; Hotta, C.; Nakazawa, M.; Minami, M. MHC class I-mediated exogenous antigen presentation by human monocytes. *Microbiol. Immunol.* 2020, 109, 274–278. [CrossRef] [PubMed]

321. Wang, J.; Ma, Y.; Long, Y.; Chen, Y. Extracellular Vesicle Derived From Mesenchymal Stem Cells Have Bidirectional Effects on the Development of Lung Cancer. *Front. Oncol.* 2022, 12, 914832. [CrossRef] [PubMed]

322. Xia, P.; Shi, Y.; Wang, X.; Li, X. Advances in the application of low-intensity pulsed ultrasound to mesenchymal stem cells. *Stem Cell Res. Ther.* 2022, 13, 214. [CrossRef]

323. Chen, L.; Qu, J.; Kalyani, F.S.; Zhang, Q.; Fan, L.; Fang, Y.; Li, Y.; Xiang, C. Mesenchymal stem cell-based treatments for COVID-19: Status and future perspectives for clinical applications. *Cell Mol. Life Sci.* 2022, 79, 142. [CrossRef]

324. Vatsa, P.; Negi, R.; Ansari, U.A.; Khanna, V.K.; Pant, A.B. Insights of Extracellular Vesicles of Mesenchymal Stem Cells: A Prospective Cell-Free Regenerative Medicine for Neurodegenerative Disorders. *Mol. Neurobiol.* 2022, 59, 459–474. [CrossRef]

325. Wu, M.C.; Meng, Q.H. Current understanding of mesenchymal stem cells in liver diseases. *World J. Stem Cells* 2021, 13, 1349–1359. [CrossRef]

326. Hassanshahi, G.; Roohi, M.A.; Esmaeili, S.A.; Pourghadamyari, H.; Nosratabadi, R. Involvement of various chemokine/chemokine receptor axes in trafficking and oriented locomotion of mesenchymal stem cells in multiple sclerosis patients. *Cytokine* 2021, 148, 155706. [CrossRef]

327. Johnson, J.; Shojaee, M.; Mitchell Crow, J.; Khamabadi, R. From Mesenchymal Stromal Cells to Engineered Extracellular Vesicles: A New Therapeutic Paradigm. *Front. Cell Dev. Biol.* 2021, 9, 705676. [CrossRef]

328. Asgari Taei, A.; Khodabakhsh, P.; Nasoohi, S.; Farahmandfar, M.; Dargahi, L. Paracrine Effects of Mesenchymal Stem Cells in Ischemic Stroke: Opportunities and Challenges. *Mol. Neurobiol.* 2022, in press. [CrossRef]

329. Ahmed, L.; Al-Massri, K. New Approaches for Enhancement of the Efficacy of Mesenchymal Stem Cell-Derived Exosomes in Cardiovascular Diseases. *Tissue Eng. Regen. Med.* 2022, in press. [CrossRef]
330. Fujii, S.; Miura, Y. Immunomodulatory and regenerative effects of MSC-derived extracellular vesicles to treat acute GVHD. Stem Cells 2022, 5, sxac057. [CrossRef]

331. Sheikholeslami, A.; Fazaei, H.; Khoshandam, M.; Kalhor, N.; Eshaghhosseini, S.J.; Sheykhhassan, M. Use of Mesenchymal Stem Cells in Crohn’s Disease and Perianal Fistulas: A Narrative Review. Curr. Stem Cell Res. Ther. 2021, in press. [CrossRef]

332. Arabpour, M.; Saghazadeh, A.; Rezaei, N. Anti-inflammatory and M2 macrophage polarization-promoting effect of mesenchymal stem cell-derived exosomes. Int. Immunopharmacol. 2021, 97, 107823. [CrossRef]

333. Botello-Flores, Y.A.; Yocupicio-Monroy, M.; Balderrabano-Saucedo, N.; Contreras-Ramos, A. A systematic review on the role of MSC-derived exosomal miRNAs in the treatment of heart failure. Mol. Biol. Rep. 2022, in press. [CrossRef] [PubMed]

334. Xiong, J.; Hu, H.; Guo, R.; Wang, H.; Jiang, H. Mesenchymal Stem Cell Exosomes as a New Strategy for the Treatment of Diabetes Complications. Front. Endocrinol. 2021, 12, 646233. [CrossRef] [PubMed]

335. Nakamura, Y.; Kita, S.; Tanaka, Y.; Fukuda, Y.; Obata, Y.; Okita, T.; Nishida, H.; Takahashi, Y.; Kawachi, Y.; Tsugawa-Shimizu, Y.; et al. Adiponectin Stimulates Exosome Release to Enhance Mesenchymal Stem-Cell-Driven Therapy of Heart Failure in Mice. Mol. Ther. 2020, 28, 2203–2219. [CrossRef]

336. Kawada-Horitani, E.; Kita, S.; Okita, T.; Nakamura, Y.; Nishida, H.; Honma, Y.; Fukuda, S.; Tsugawa-Shimizu, Y.; Kozawa, J.; Sakaue, T.; et al. Human adipose-derived mesenchymal stem cells prevent type 1 diabetes induced by immune checkpoint blockade. Diabetologia 2022, 65, 1185–1197. [CrossRef]

337. Xu, H.Y.; Li, N.; Yao, N.; Xu, X.F.; Wang, H.X.; Liu, X.Y.; Zhang, Y. CD8+ T cells stimulated by exosomes derived from RenCa cells mediate specific immune responses through the FasL/Fas signaling pathway and, combined with GM-CSF and IL-12, enhance the anti-renal cortical adenocarcinoma effect. Oncol. Rep. 2019, 42, 866–879. [CrossRef]

338. Qin, Q.; Song, R.; Du, P.; Gao, C.; Yao, Q.; Zhang, J.A. Systemic Proteomic Analysis Reveals Distinct Exosomal Protein Profiles in Rheumatoid Arthritis. J. Immunol. Res. 2021, 2021, 2021. [CrossRef]

339. Takamura, Y.; Aoki, W.; Satomura, A.; Shibasaki, S.; Ueda, M. Small RNAs detected in exosomes derived from the MH7A synovial fibroblast cell line with TNF-α stimulation. PLoS ONE 2018, 13, e0201851. [CrossRef]

340. Hosseini, R.; Sarvaz, 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]

341. Ponath, V.; Hoffmann, N.; Bergmann, L.; Mäder, C.; Alashkar, A.B.; Preußer, C.; Pogge von Strandmann, E. Secreted Ligands of the NK Cell Receptor NKP30: B7-H6 Is in Contrast to BAG6 Only Marginally Released via Extracellular Vesicles. Int. J. Mol. Sci. 2021, 22, 2189. [CrossRef]

342. Ferguson Bennit, H.R.; Gonda, A.; Kabagwira, J.; Oppegard, L.; Chi, D.; Licero Campbell, J.; De Leon, M.; Wall, N.R. Natural Killer Cell Phenotype and Functionality Affected by Exposure to Extracellular Survivin and Lymphoma-Derived Exosomes. Int. J. Mol. Sci. 2021, 22, 12157. [CrossRef]

343. Zhu, X.; Qin, X.; Wang, X.; Wang, Y.; Cao, W.; Zhang, J.; Chen, W. Oral cancer cell-derived exosomes modulate natural killer cell activity by regulating the receptors on these cells. Int. J. Mol. Med. 2020, 46, 2115–2125. [CrossRef]

344. Jafarzadeh, N.; Safari, Z.; Norouzian, M.; Amirizadeh, N.; Forouzandeh, M.M.; Sadeghizadeh, M. Alteration of cellular and immune-related properties of bone marrow mesenchymal stem cells and macrophages by K562 chronic myeloid leukemia cell derived exosomes. J. Cell Physiol. 2019, 234, 3697–3710. [CrossRef]

345. Koh, E.; Lee, E.J.; Nam, G.H.; Hong, Y.; Cho, E.; Yang, Y.; Kim, I.S. Exosome-SIRPα, a CD47 blockade increases cancer cell phagocytosis. Biomaterials 2017, 121, 121–129. [CrossRef]

346. Du, J.; Wan, Z.; Wang, C.; Lu, F.; Wei, M.; Wang, D.; Hao, Q. Designer exosomes for targeted and efficient ferroptosis induction in cancer via chemo-photodynamic therapy. Theranostics 2021, 11, 8185–8196. [CrossRef] [PubMed]

347. Shimizu, A.; Sawada, K.; Kobayashi, M.; Yamamoto, M.; Yagi, T.; Kinose, Y.; Kodama, M.; Hashimoto, K.; Kimura, T. Exosomal CD47 Plays an Essential Role in Immune Evasion in Ovarian Cancer. Mol. Cancer Res. 2021, 19, 1583–1595. [CrossRef]

348. Kamerkar, S.; LeBlue, V.; 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]

349. Yan, J.; Liu, X.; Wu, F.; Ge, C.; Ye, H.; Chen, X.; Wei, Y.; Zhou, R.; Duan, S.; Zhu, R.; et al. Platelet Pharmacytes for the Hierarchical Amplification of Antitumor Immunity in Response to Self-Generated Immune Signals. Adv. Mater. 2022, 34, e2109517. [CrossRef] [PubMed]

350. Rolfsé, V.; Ídel, C.; Fries, R.; Plötte-Martin, K.; Habermann, J.; Gemoll, T.; Bohnet, S.; Latz, E.; Ribbat-Ídel, J.; Franklin, B.; et al. PD-L1 is expressed on human platelets and is affected by immune checkpoint therapy. Oncotarget 2018, 9, 27460–27470. [CrossRef] [PubMed]

351. Ningen, H.; Chen, H.; Deng, J.; Xiao, C.; Xu, M.; Shan, L.; Yang, C.; Zhang, Z. Exosomes secreted by FNDCS5-BMMS cells protect myocardial infarction by anti-inflammation and macrophage polarization via NF-κB signaling pathway and Nrf2/抗氧化-1 axis. Stem Cell Res. Ther. 2021, 12, 519. [CrossRef]

352. Li, C.; Li, X.; Shi, Z.; Wu, P.; Fu, J.; Tang, J.; Qing, L. Exosomes from LPS-preconditioned bone marrow MSCs accelerated peripheral nerve regeneration via M2 macrophage polarization: Involvement of TSG-6/NF-κB/NLRP3 signaling pathway. Exp. Neurol. 2022, 356, 114139. [CrossRef]
353. Hu, Y.; Qu, H.; He, J.; Zhong, H.; He, S.; Zhao, P.; Zhang, L.; Chen, J.; Deng, C. Human placental mesenchymal stem cell derived exosomes exhibit anti-inflammatory effects via TLR4-mediated NF-κB/MAPK and PI3K signaling pathways. *Pharmazie* 2022, 77, 112–117. [CrossRef]

354. Fan, L.; Dong, J.; He, X.; Zhang, C.; Zhang, T. Bone marrow mesenchymal stem cells-derived exosomes reduce apoptosis and inflammatory response during spinal cord injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway. *Hum. Exp. Toxicol.* 2021, 40, 1612–1623. [CrossRef]

355. Mentkowski, K.I.; Mursleen, A.; Snitzer, J.D.; Euscher, L.M.; Lang, J.K. CDC-derived extracellular vesicles reprogram inflammatory macrophages to an arginase 1-dependent proangiogenic phenotype. *Am. J. Physiol. Heart Circ. Physiol.* 2020, 318, H1447–H1460. [CrossRef]

356. Hattori, H.; Takaoka, K.; Ueta, M.; Oshitani, M.; Tamaoka, J.; Noguchi, K.; Kishimoto, H. Senescent RAW264.7 cells exhibit increased production of nitric oxide and release inducible nitric oxide synthase in exosomes. *Mol. Med. Rep.* 2021, 24, 681. [CrossRef] [PubMed]