MINI-REVIEW

Extracellular vesicle-coated nanoparticles

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Abstract

Synthetic nanoparticles have been used for a variety of theranostic applications to aid in the betterment of human health. These nanoparticles can provide platforms for targeted imaging and therapy of diseased tissues. The development of surface coatings for nanoparticles has enabled their selective uptake in tissues of interest, and the use of membrane-derived nanoparticle coatings provides a particularly promising approach for the regulation of nanoparticle-tissue interactions. Membranous extracellular vesicles (EVs) secreted by cells have been known to contain antigens, proteins, and other cell components on their surface that facilitate their uptake in target cells, enabling the transport of information from one cell to another. EV-based nanoparticle coatings allow for the expansion of nanoparticle targeting from typical approaches that target individual antigens, to an approach that can simultaneously target many antigens for more efficient uptake within target cells. EV-derived coatings also possess immune evasive properties that can lead to increased circulation time. In this mini-review, we describe the various approaches and applications for EV coating of nanoparticles, a majority of which focus on cancer applications. We also provide an overview of commonly used EV sources for nanoparticle coating applications.

KEYWORDS
cancer, coating, encapsulation, exosomes, extracellular vesicles, nanoparticles

INTRODUCTION

Healthy and diseased cells secrete extracellular vesicles (EVs) that are composed of a lipid bilayer as well as antigens, intracellular proteins, proteases, miRNA, and mRNA from the cells from which they were shed.\textsuperscript{1-6} EVs range in size from several nm to several \( \mu \)m and can be referred to as microparticles, microvesicles, ectosomes, or exosomes accordingly.\textsuperscript{7} The contents of these EVs vary based on the origin and target cells, and allow for transport of signals...
from one cell to another. In recent years, there has been growing interest in the use of EVs for diagnostic and therapeutic applications. A number of other review papers have described applications of exosomes and EVs in drug delivery, immunotherapy, and other biomedical applications, with a majority focusing on applications in cancer. The presence of specific antigens from the source cells on the surfaces of EVs has typically been found to allow for specific uptake of EVs within that cell type. For example, cancer cell-derived exosomes have commonly been used to encapsulate drugs, thus increasing the delivery efficiency of these therapeutic moieties to cancer tumors.

At the same time, synthetic nanoparticles have long served as therapeutic and imaging agents, enabling targeted imaging and treatment of diseases such as cancer and atherosclerosis. A number of publications describe the use of cell membrane-derived coatings to enable nanoparticle targeting. The use of EV-derived coatings to facilitate nanoparticle uptake is a logical progression of membrane-derived coatings, and takes advantage of EV surface antigens for uptake within cells of interest. The goal of this mini-review is to explore examples of EV-coated nanoparticles and provide insight into their use. We begin by reviewing common EV sources and types of synthetic nanoparticles upon which EV coatings are generated. We then describe the major approaches to generate EV coatings on nanoparticle surfaces. Afterwards, we describe the many approaches that have taken advantage of EV-coated nanoparticles for cancer therapy. Lastly, we describe the applications of EV-coated nanoparticles for diseases aside from cancer, and provide a perspective on the future direction of research on EV-coated nanoparticles. An overview of common EV sources, coating methods, and applications are provided in Figure 1.

2 EXTRACELLULAR VESICLES AS VERSATILE COATINGS FOR NANOPARTICLES

EVs have emerged as versatile coatings for synthetic nanoparticles, enabling selective uptake in tissues of interest. In this section, we explore EV and nanoparticle compositions, coating methods, and applications.

2.1 Common EV sources and types of synthetic nanoparticles

Cancer cells and mesenchymal stem cells (MSCs) are the most commonly utilized exosome sources for nanoparticle coatings. Beyond these, EV-based nanoparticle coatings have also been derived from human umbilical vein endothelial cells (HUVECs), macrophages, and bacterial cells. To date, a majority of the nanoparticles coated with exosomes have been metallic in nature, including gold nanoparticles, iron oxide nanoparticles, (IONs) and gold-IONs (GIONs). However, there have been a few examples of poly(lactic-co-glycolic acid) (PLGA) nanoparticles and metal organic framework (MOF) nanoparticles coated with exosomes.

2.2 Coating methods

The coating methods for EVs on nanoparticle surfaces are similar to those of cell membranes on nanoparticle surfaces. Four major approaches are used for the encapsulation of synthetic nanoparticles in EVs. The most common approach is the direct incubation of cells with medium containing the synthetic nanoparticles. The nanoparticles are then internalized by the cells and secreted within exosomes, taking advantage of the exosomal biogenesis pathway. The three remaining approaches involve the physical mixing of pre-collected exosomes with the synthetic nanoparticles. The nanoparticles are then internalized by the cells and secreted within exosomes, taking advantage of the exosomal biogenesis pathway. The three remaining approaches involve the physical mixing of pre-collected exosomes with the synthetic nanoparticles. In one approach, the direct mixing of exosomes with synthetic nanoparticles leads to their encapsulation with time. In another approach, the nanoparticle-exosome mixture is sonicated, leading to the formation of an exosome coating on the nanoparticle surface. This approach has been especially popular in the coating of soft nanoparticles with exosomes. In the final approach, the nanoparticle-exosome mixture is extruded through porous membranes, leading to the formation of exosome-coated nanoparticles. We previously used electroporation to enhance the entry of nanoparticles into cell membranes. Despite the years of work in this field, the ideal coating method remains a topic of debate, with some claiming that the use of the exosomal biogenesis pathway leads to low encapsulation efficiency. In contrast, Sancho-Albero et al conducted a comprehensive evaluation of B16-F10 murine melanoma exosome coatings on hollow gold nanoparticles, finding that pre-incubation of the cells with the nanoparticles had an effect on EV nanoparticle load, photosensitizer load, size, yield, purity, and phototoxicity. However, the advantages and disadvantages of each coating method may depend on the specific nanoparticle type and intended application. Piffoux et al found that the methods by which iron oxide nanoparticles were loaded into HUVEC EVs had an effect on EV nanoparticle load, photosensitizer load, size, yield, purity, and phototoxicity. For example, spontaneously-released EVs had higher yield but lower purity than EVs released under starvation. Thus, although a variety of reported methods exist for coating nanoparticles with EVs, the factors that make one method more favorable than another method...
Applications in cancer

2.3.1 Cancer-derived EVs

A common approach involves the use of coatings derived from cancer cell EVs for specific uptake in that same type of cancer cells. Many studies have demonstrated this specific uptake in vitro. For example, Illes et al coated MOF nanoparticles (NPs) with exosomes from HeLa cells. They demonstrated that the coated MOF NPs were taken up within HeLa cells, enabling delivery of the anticancer drug suberoylbishydroxamic acid. Dumontelet al coated zinc oxide nanocrystals (ZnO NCs) with EVs derived from KB (CCL17) cancer cells. They evaluated various parameters for encapsulation within EVs, including the coupling temperature and time, mixing method, type of dispersing medium, and ratio between EVs and ZnO NCs. They then demonstrated that ZnO NCs encapsulated within EVs were taken up by KB cancer cells and induced toxicity within them. Sancho-Albero et al coated hollow gold nanoparticles (HGNs) with exosomes derived from B16-F10 murine melanoma cells, finding that pre-incubation
of cells with PEGylated HGNs took advantage of exosomal biogenesis and was the most efficient encapsulation method, resulting in 50% of exosomes being loaded with HGNs. They then demonstrated that exosome-encapsulated HGNs were taken up by B16-F10 cells and could be used for photothermal therapy. Sancho-Albero et al have also demonstrated the assembly of palladium nanosheets directly within cancer cell exosomes, using them to deliver catalytic cargo directly to cancer cells.

Since breast cancer tumors often metastasize to the lungs, Roma-Rodrigues et al used exosome-coated nanoparticles to regulate the communication between breast cancer cells and bronchial-tracheal epithelial (BTE) cells. MCF-7 breast cancer cells were incubated with gold nanoparticles functionalized with anti-RAB27A. This modulated the expression of RAB27A and decreased exosome secretion from the MCF-7 cells. When the exosomes derived from cells treated with gold nanoparticles functionalized with anti-RAB-27A were then exposed to BTE cells, they led to lower expression of C-Myc, an oncogene that is overexpressed in breast cancer. These findings indicate that exosome-coated nanoparticles can be transported from one cell type to another, and can be used not only for direct delivery of signals to cancer cells, but also potentially to prevent the spread of tumor cells to other organs.

Other reports have expanded these investigations to in vivo use. Cheng et al utilized MOF NPs, loading them with proteins and then self-assembling the membranes from MDA-MB-231-derived EVs onto the NP surfaces. They demonstrated that EV coatings reduced particle uptake by macrophages, and led to greater uptake by MDA-MB-231 cells compared to uptake by 293T human embryonic kidney cells, 3T3 mouse embryo fibroblasts, CAD mouse central nervous system-derived cells, MCF-7 human breast adenocarcinoma cells, and SH-SY5Y human neuroblastoma cells. After intravenous administration, coated MOF NPs had higher accumulation in orthotopic MDA-MB-231 xenograft tumors in mice than non-coated MOF NPs, and led to greater transduction of the loaded proteins. The therapeutic efficacy of loaded gelonin was also increased as a result of NP coating. In another approach that utilized breast cancer-derived exosomes to treat breast cancer, Bose et al sought to target miR-21, which is overexpressed in cancer cells and can lead to chemotherapy resistance. They generated Cy5-anti-miR-21 packed EVs by exposing 4T1 cells to Cy5-anti-miR-21 in situ and then collecting the EVs. The Cy5-anti-miR-21 packed EVs were found to reduce resistance to doxorubicin. They then coated GIONs with the Cy5-anti-miR-21 packed EVs to allow for magnetic resonance (MR) contrast and photothermal properties. In vivo experiments in a syngeneic subcutaneous 4T1 tumor-bearing mouse model demonstrated that the particles accumulated at the tumor site, delivered anti-miR-21, and led to inhibited tumor growth and increased doxorubicin therapeutic efficacy.

Liu et al developed a microfluidic device that uses ultrasonication to coat NPs with membranes from EVs, membranes from cancer cells, or lipid membranes. They isolated EVs and cell membranes from A549 human lung carcinoma cells, and coated PLGA nanoparticles with the membranes using the microfluidic ultrasonication method. When administered in vivo in A549 tumor-bearing mice, EV-coated PLGA NPs had higher circulation times than those coated with membranes from cancer cells, and were found to evade immune cells, thus leading to better delivery to tumor cells. The specific in vivo uptake of EV-coated PLGA NPs was also demonstrated by comparing their uptake in A549 tumors with their uptake in MDA-MB-231 tumors. Han et al expanded this work to use an aptamer coating layer on top of MDA-MB-231 EV-coated PLGA NPs, leading to enhanced tumor targeting.

In contrast to reports that emphasize the specific uptake of EV-coated nanoparticles within one target cell type, Yong et al demonstrated cross-reactivity between exosomes from different cancer types. They loaded porous silica nanoparticles with doxorubicin (Dox-PSiNPs), and then coated the Dox-PSiNPs with exosomes from H22, Bel7402, and B16-F10 cancer cell lines by incubation with the cells and subsequent exocytosis (exosomal biogenesis pathway). They demonstrated that exosome coatings from tumor cells increased the nanoparticle uptake in cells, and that the coated particles were also taken up by cancer stem cells isolated from the cell lines. However, the exosome coatings were found to be cross-reactive between different cell types, with high uptake of H22 exosome-coated Dox-PSiNPs in B16-F10 cells and vice versa. This cross-reactivity was further utilized in vivo, where H22-derived Dox-PSiNPs injected in 4T1 tumor-bearing mice had strong anticancer properties and led to decreased tumor volume and a reduction in cancer stem cells. Additionally, they demonstrated that particles coated with exosomes from HUVECs had less uptake in the H22 cells, and vice versa, which indicates a preferential uptake of cancer-derived exosomes in cancer cell lines.

### 2.3.2 Other types of EVs

In addition to using cancer cell-derived exosomes for cancer applications, other approaches have utilized exosomes derived from tumor-homing non-cancerous cells for cancer applications. Since MSCs have been known to have tumor-homing properties, Altanerova et al used exosomes from MSCs that expressed the yeast cytosine deaminase::uracil phosphoribosyl transferase
suicide fusion gene in the presence of the prodrug 5-
fluorocytosine (5-FC). Incubation of the MSCs with
venofer IONs led to the secretion of exosomes containing
iron oxide, which were then used to cause the death of
PC3 and HeLa cells via alternating magnetic field-induced
intracellular hyperthermia or by exposure to the 5-FC
prodrug. Macrophages are another class of cells known to
be recruited by tumors, and Xiong et al utilized RAW 264.7
macrophage-secreted exosomes to coat nanoparticles
that were composed of a laurate-functionalized Pt(IV)
prodrug, human serum albumin, and lecithin.46 This
led to prolonged blood circulation of the nanoparticles,
enabled their uptake at the orthotopic 4T1 tumor site and
metastatic breast cancer lung nodules, and allowed for
administration of platinum-based chemotherapy. Piffoux
et al incubated iron oxide nanoparticles with HUVECs,
producing nanoparticle-loaded exosomes by starving
the cells.35 The coated nanoparticles were then used
for photodynamic therapy of PC3 prostate cancer cells.
They also evaluated the effects of exosome production
method on the trade-off between EV nanoparticle load,
photosensitizer load, size, yield, purity, and phototoxicity.

2.4 Other applications

Another application of EV-coated nanoparticles is neu-
roimaging. Betzer et al encapsulated glucose-coated GNRs
with human MSC exosomes through direct incubation
of the nanoparticles with the exosomes.35 They demon-
strated that nanoparticle size, incubation temperature,
and the presence of a glucose coating on the nanoparticle
surface played a role in successful encapsulation within
exosomes. The gold nanoparticles provided CT con-
trast, allowing for visualization of exosome-encapsulated
nanoparticle accumulation at the stroke region in C57BL/6
mice brains after acute striatal stroke. The colocalization
of nanoparticles with exosomes was also confirmed
using ex vivo fluorescence imaging of mice treated with
double-labeled exosomes (exosome + GNRs + PKH26 dye).
Despite these promising results, Qu et al raised concerns
about the nanoparticle encapsulation method within the
exosomes, proposing that the centrifugation step would
not allow for separation of GNRs from exosome-coated
GNRs.47 In another neuroimaging application, Khongkow
et al developed AuNPs coated with exosomes from
transformed human embryonic kidney cells (HEK293T)
transfected to express RVG-Lamp2b fusion proteins and
target neuronal cells.48 They demonstrated that these
coated AuNPs adhered to brain cells under laminar flow.
The transport of particles across the blood-brain-barrier
was demonstrated in an in vitro model, as well as through
in vivo bioluminescence imaging of mouse brains after
intravenous administration of the particles. These studies
demonstrated that RVG-targeted exosomes had higher
accumulation in the brain than those not targeted with
RVG, further cementing the role of cell and exosome
surface proteins on the utility of secreted exosomes in
nanoparticle targeting applications.

In a unique approach, Gao et al coated PLGA nanopar-
icles with EVs from S. Aureus bacteria.49 They found
that the bacterial EV-coated nanoparticles had preferential
uptake in macrophages exposed to that particular type of
bacteria. Thus, PLGA nanoparticles coated with EVs from
S. aureus had preferential uptake in macrophages exposed
to S. aureus, while those coated with EVs from E. coli had
preferential uptake in macrophages exposed to E. Coli.
PLGA nanoparticles coated with EVs from S. Aureus had
high uptake in vivo in tissues that had S. aureus infections,
enabling the delivery of antibiotics to the site of infections.

Sancho-Albero et al further demonstrated that coating
nanoparticles with exosomes from MSCs led to preferen-
tial uptake by MSCs compared to uptake in B16F1 cells,
B16-F10 cells, and monocytes.50 A summary of various EV-
coated nanoparticles is provided in Table 1.

3 CONCLUSIONS

EV-coated nanoparticles represent a relatively new
approach for targeted delivery of therapeutic and imaging
agents to tissues of interest. In recent years, the field of
EV-coated nanoparticles has greatly expanded, and many
different coating approaches and nanoparticle types have
been used for applications spanning cancer therapy, neu-
roimaging, and treatment of bacterial infections. Despite
this progress, further studies must be conducted to clarify
key areas of ambiguity within the field. The uncertainty
over the best method for nanoparticle encapsulation
within EVs remains a major obstacle to the widespread
adoption of EV coating as a simple targeting approach
for nanoparticles. The general disagreement within the
field suggests that the ideal encapsulation method may
vary based on nanoparticle type and cell type. Thus,
extensive studies that evaluate multiple nanoparticle types
(including “soft” and “hard” nanoparticles) and a variety
of cell lines can be undertaken in order to provide a clear
understanding of the parameters that make each type
of encapsulation method ideal for some scenarios. Fur-
thermore, the specific uptake of EV-coated nanoparticles
within the cell line from which the EVs were derived must
be further explored. Reports of cross-targeting between
different cell types appear to be in conflict with some
reports of specific uptake within the cells from which
the EVs were derived. It is clear that the characteristics
of each cell type govern the behavior of its EVs, and
| Targeted disease          | EV/Exosome source | Nanoparticle type | Coating method               | Application                                      | Advantage                                                                 | Reference       |
|--------------------------|-------------------|-------------------|------------------------------|--------------------------------------------------|---------------------------------------------------------------------------|-----------------|
| Cervical cancer          | HeLa cervical cancer cells | MIL-88a MOF nanoparticles | Incubation of exosomes with MOF NPs | SBHA delivery to HeLa cells                      | Specific uptake and targeted drug delivery                                | Illes et al[36] |
| Cervical cancer          | KB cell line (CCL17) | ZnO nanocrystals | Incubation of EVs with ZnO NCs | Cell-specific uptake and toxicity in KB cells    | Specific uptake for toxicity to cancer cells                              | Dumontel et al[37] |
| Melanoma                 | B16-F10 murine melanoma cells | PEGylated hollow gold nanoparticles (HGNs) | Many tested; incubation of cells with nanoparticles found to be most efficient | Uptake by B16-F10 cells, photothermal therapy | Specific uptake enabling targeted photothermal therapy                    | Sancho-Albero et al[34] |
| Breast cancer            | MDA-MB-231 breast cancer cells | ZIF-8 MOF nanoparticles | Sonication and extrusion | Therapeutic protein delivery to MDA-MB-231 tumors in mice | Immune evasion and improved uptake leading to greater protein transduction and therapeutic efficacy | Cheng et al[40] |
| Breast cancer            | 4T1 murine breast cancer cells exposed to Cy5-anti-miR-21 | gold–iron oxide nanoparticles (GIONs) | Extrusion through membranes | in vitro photothermal therapy, MR imaging, reduce doxorubicin resistance in 4T1 tumor-bearing mice | High accumulation at tumor site, enabling targeted imaging and enhanced therapeutic efficacy | Bose et al[42] |
| Breast cancer            | MCF-7 cells         | Gold nanoparticles functionalized with anti-RAB27A | Incubation of cells with nanoparticles | Regulation of C-Myc expression in bronchial/tracheal epithelial cells | Down-regulation of pro-metastatic signals                                  | Roma-Rodrigues et al[39] |
| Lung cancer              | A549 human lung carcinoma cells | PLGA nanoparticles | Microfluidic sonication | Increased circulation time, immune evasion, specific uptake in A549 tumors | Immune evasion and longer circulation                                       | Liu et al[42] |
| Breast cancer            | MDA-MB-231 cells | PLGA nanoparticles | Microfluidic sonication and aptamer coating | Increased MDA-MB-231 targeting efficiency | Improved tumor targeting                                                  | Han et al[42] |
| Hepatocarcinoma and breast cancer | H22, Bel7402, and B16-F10 cell lines | Dox-loaded porous silica nanoparticles (Dox-PSiNPs) | Incubation of cells with nanoparticles | Drug delivery, reduction in mouse tumor size, and decrease in number of cancer stem cells | Increased uptake in cancer cells and cross-reactivity between different cancer types | Yong et al[44] |
| Prostate cancer and cervical cancer | MSCs expressing the yCD::UPRT gene in the presence of 5-fluorocytosine | Venofer (iron oxide nanoparticles) | Incubation of cells with nanoparticles | Cell death via AMP-induced intracellular hyperthermia and prodrug-induced expression of yCD::UPRT gene | Enabling prodrug-triggered cancer cell death                                | Altanerova et al[45] |

(Continues)
| Targeted disease | EV/Exosome source | Nanoparticle type | Coating method | Application                                                                 | Advantage                                                                 | Reference |
|------------------|-------------------|-------------------|---------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------|
| Breast cancer    | RAW 264.7 macrophage cells | Laurate-functionalized Pt(IV) prodrug, human serum albumin, and lecithin | Sonication | Increased nanoparticle circulation, uptake and chemotherapy in orthotopic breast cancer tumors and lung metastases in mice | Prolonged circulation and recruitment to tumor metastases                  | Xiong et al |
|                  |                   |                   |               |                                                                            |                                                                            |           |
| Prostate cancer  | HUVECs            | Iron oxide nanoparticles | Incubation of cells with nanoparticles | Uptake in prostate cancer cells, photodynamic therapy | Enabled systematic evaluation of coating method on therapeutic efficacy | Piffoux et al |
|                  |                   |                   |               |                                                                            |                                                                            |           |
| Stroke           | Human MSCs        | Gold nanoparticles | Incubation of exosomes with GNP | Visualization of stroke region in mice brains | Increased accumulation at stroke regions | Betzer et al |
|                  |                   |                   |               |                                                                            |                                                                            |           |
| N/A              | Transformed human embryonic kidney cells (HEK293T) | Gold nanoparticles | Extrusion through membranes | Passage of nanoparticles across blood-brain-barrier in mice | Crossing the blood-brain barrier | Khongkow et al |
|                  |                   |                   |               |                                                                            |                                                                            |           |
| S. Aureus infection | S. Aureus bacteria | PLGA              | Sonication | Delivery of antibiotics to infection sites in vivo | Targeted uptake at infection sites | Gao et al |
|                  |                   |                   |               |                                                                            |                                                                            |           |
| N/A              | Human placental MSCs | PEGylated hollow gold nanoparticles (HGNs) | Incubation of cells with nanoparticles | Specific uptake in MSCs, light-induced hyperthermia | Targeted uptake | Sancho-Albero et al |

Some similar properties may exist across different cell types (for example, multiple cancer cell lines) that allow for cross-reactivity between different cell types. These properties must be systematically studied, and clear benchmarks must be developed to indicate the cutoff between cross-reactivity and selective uptake.

The use of EV coatings on nanoparticles will likely continue to grow with time, potentially one day taking the place of common targeting methods such as those using antibodies, peptides, or aptamers. One approach that will likely see increased application in upcoming years is the encapsulation of nanoparticles in EVs that have been engineered for increased surface expression of proteins and antigens of interest. Additionally, the use of EV coatings on nanoparticle surfaces will likely be further expanded from focusing on typical well-known particles to being used as a strategy for targeting novel nanoparticles to tissues of interest. Furthermore, applications of EV-coated nanoparticles can be expanded from primarily cancer applications to other applications in which targeted delivery of therapeutic and imageable nanoparticles can be utilized. The immune-evasive and immune-activating properties of EVs may also be further exploited for use in immunomodulatory nanoparticle-based therapies. These properties may be especially important in the development of personalized EV-based therapies that can utilize patient-derived EVs. At the same time, the scalability of EV-based therapies must also be considered, as any therapy that depends on the isolation of EVs from patient samples will be limited by the number of EVs that are produced within, and isolated from, the tissues of interest. In addition, potential negative effects from long-term accumulation of EV-coated nanoparticles in vivo can be explored. Long-term studies must be conducted to ensure that the lengthened retention of EV-coated nanoparticles does not lead to negative consequences such as liver toxicity.

**CONFLICT OF INTEREST**
The authors declare no conflict of interest.

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