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Critical Review

Impact of Radiation on Exosomes in Regulating Tumor Immune Microenvironment

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Purpose: Exosomes have been shown to play a role in most, if not all, steps of cancer progression. We still lack a comprehensive understanding of the bidirectional communication of exosomes between tumor cells and immune cells. This article aims to explore how exosomes can influence cancer growth and how they are affected by radiation therapy.

Methods and Materials: We searched on PubMed and Web of Science on the impact of radiation on tumor derived exosomes and immune cell derived exosomes in tumor immune microenvironment. We screened all the related articles and summarized their main discoveries and important results.

Results: This article reviewed the effects of tumor derived exosomes and immune cell-derived exosomes on TME and tumor progression after radiotherapy, suggesting the dual effects of exosomes which may refer to clinical practice. Moreover, we retrospected the clinical applications based on tumor derived exosomes, including liquid biopsy, radio-resistance and drug delivery, and discussed the challenges and prospects.

Conclusions: Exosomes are important in cancer treatment, especially with radiation therapy. Learning more about them could lead to better treatments. However, there are still challenges to overcome. The review points out the need for more research in this area.

Exosomes, a special class of extracellular vesicles, are nano-sized vesicles with a diameter of 40 to 160 nm. The biogenesis of exosomes involves the double invagination of the plasma membrane and the formation of intracellular multivesicular bodies, which contain vesicles that are future exosomes.[1] Multivesicular bodies have 2 destinations: fusing with lysosomes or autophagosomes for degradation or with the plasma membrane to release intraluminal vesicles, namely exosomes.[2,3] Studies have shown that exosomes are associated with immune responses, viral pathogenicity, cardiovascular diseases, central nervous system−related diseases, and tumor progression.[4] The reason is that exosomes can contain many constituents of a cell, such as DNA, RNA, lipids, metabolites, and proteins (both cytosolic and cell-surface). These components can effectively alter biological responses of recipient cells, thereby promoting or restraining certain pathophysiological processes. Among them, the activation and response of immune cells are closely associated with

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tumor growth, progression, and/or metastasis. These immune cells frequently infiltrate tumor tissues and interact with tumor and stromal cells, many of which are mediated by exosomes.

Tumor-derived exosomes (TDEs) can carry and transfer a variety of molecules to immune cells, thus exerting effects by changing the phenotype, inhibiting functions, enabling immune escape, and ultimately changing the tumor immune microenvironment. In terms of phenotype, TDEs were reported to induce M2 polarization of macrophages by delivering microRNAs (miRNAs) to macrophages, and these miRNAs could regulate the PTEN signaling pathway in different types of cancers, which results in tumor growth and metastasis.[5-7] TDEs were also found to inhibit the differentiation of dendritic cells (DCs) from myeloid precursor cells or myeloid-derived suppressor cells by releasing interleukin-6 (IL-6), heat shock protein 70 (HSP70), HSP72, human leucocyte antigen-G (HLA-G), etc, contributing to an immunosuppressive effect.[8-10] Moreover, TDEs could modulate immune cells' activation by regulating the secretion of cytokines. For example, hepatocellular carcinoma −derived exosomal circular ubiquitin-like with PHD and ring finger domain 1 RNA (circUHRF1) decreases natural killer (NK) cell proportion and tumor infiltration,[11] and non-small cell lung cancer (NSCLC)−derived exosomal circular ubiquitin-specific protease-7 (circUSP7) indicates cytotoxic T lymphocyte dysfunction.[12] Besides, it has long been discovered that tumor-derived exosomal PD-L1 inhibits CD8+ T cell activity and promotes immune escape,[13,14] which has led to a great many clinical studies and applications on anti-PD-1/PD-L1 drugs, such as durvalumab, atezolizumab, and pembrolizumab.

Conversely, immune cells can also release exosomes to modulate tumor microenvironment (TME) by playing immunostimulatory or immunosuppressive roles. Several studies have pointed out that exosomes derived from antigen-presenting cells regulate T cell functions and eventually affect tumor growth. For instance, DC-derived exosomes can induce a strong antigen-specific immune response and slow down heterogeneous tumor.[15] On the other hand, tumor-associated macrophages (TAMs)[16] and regulatory T cells (Tregs)[17,18] generally exert immunosuppressive functions by transmitting their immunosuppressive cargoes. TAM-derived exosomes participate in the immune escape of tumor cells via exosomal miR-155-5p[19] or exosomal miR-29a-3p.[20] Similarly, Treg-derived exosomal IL-35 limits infiltration and promotes the exhaustion of T cells in the TME.[21,22] Treg-derived exosomal miRNAs can also inhibit type 1 T helper cell proliferation and cytokine release,[23] and exosomal miR-21 downregulates the expression of paternally expressed gene 3 to promote the survival, proliferation, migration, and invasion of glioma cells.[24] Taken together, these results indicate that exosomes mediate the interaction between TAMs, Tregs, and T cells, contributing to an immunosuppressive microenvironment that assists tumor progression and metastasis.

Mature application of radiation therapy (RT) has been involved in treatments of numerous solid tumors. RT induces immunogenicity in cancer cells through the DNA damage response, leading to the accumulation of cytosolic double-stranded DNA (dsDNA). It can also exert direct cytotoxic effects on tumor cells and reprogram the TME to an immunostimulatory state by promoting tumor antigen transfer, priming effector T cells, and increasing the number of NK cells.[25] Accumulating evidence suggests that radiation has the potential to mediate the communication between exosomes and immune cells. RT has been found to convert the phenotype, affect the cytokines, and change the activation degree of immune cells via exosomes derived from irradiated tumor cells,[26-28] which eventually adjusts tumor growth. Moreover, exosomes derived from irradiated immune cells are also found to participate in intercellular communication and tumor progression. This review will focus on how radiation alters the effect of exosomes (both tumor cell−derived and immune cell−derived) in TME and the therapeutic significance of exosomes. The mechanisms underlying these procedures are being identified and may eventually lead to clinical application.

Radiation-Induced Changes in the Immune System

Irradiated TDEs convert immune responses

Irradiated tumor cells increase the immunogenicity of the tumor and alter the properties of immune cells-Fig. 1. In terms of DCs, Diamond et al[26] found that exosomes derived from irradiated mouse breast cancer (BC) cells (ie, RT-TDEs) could transfer dsDNA to DCs and stimulate the upregulation of various cytokines, ultimately enhancing T cell responses. To be specific, internal dsDNA of RT-TDEs triggers IFN-I secretion of DCs, whereas 3-prime repair exonuclease 1 (TREX1) expression in parental cells degrades internal dsDNA, thus inhibiting IFN-I secretion. When coculturing DCs with RT-TDEs, DCs were significantly activated via the STING pathway, showing increased surface molecules (CD40, CD80, and CD86), as well as IFN-β secretion, thereby inducing DC activation and T cell antitumor response. In vivo, RT-TDEs can be phagocytosed by DCs in lymph nodes and induce tumor-specific CD8(+) T cell responses. In addition, RT-TDEs protected mice from tumor development significantly better than unirradiated TDEs in a prophylactic vaccination experiment. Another research[27] demonstrated that gamma-irradiated melanoma cancer cell−derived exosome upregulated the nuclear protein high mobility group box 1 itself, as well as the expression of surface

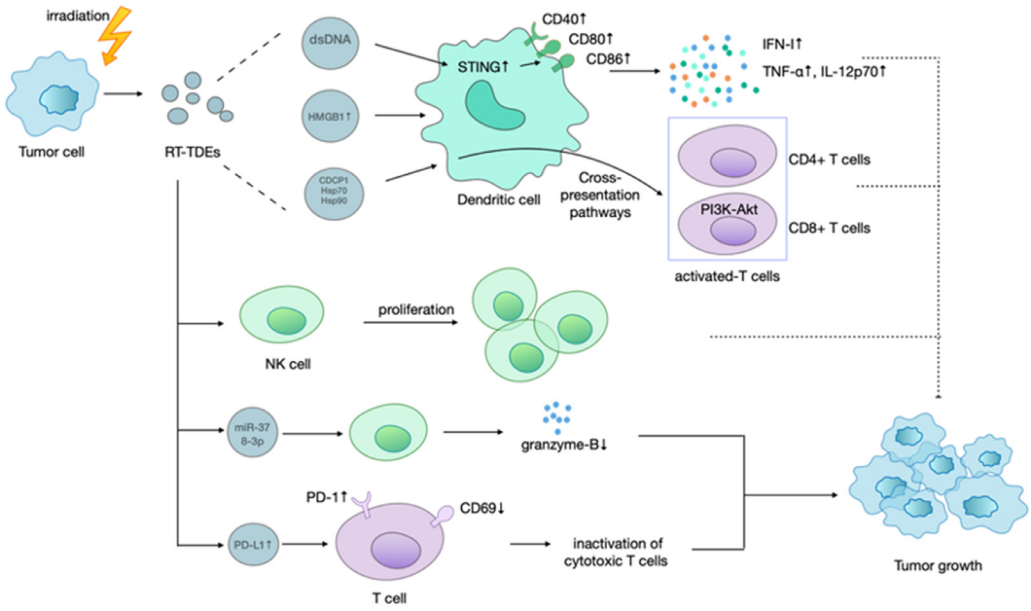

Figure 1 The effect of radiation therapy tumor-derived exosomes (RT-TDEs) on immune cells. Exosomes derived from irradiated tumor cells (RT-TDEs) could transfer double-stranded DNA (dsDNA) to dendritic cells (DCs) and then trigger IFN-I secretion of DCs and upregulation of surface molecules (CD40, CD80, and CD86), ultimately enhancing T cell responses. RT-TDEs also upregulated HMGB1, as well as TNF-α and IL-12p70 in DCs, thus promoting T cell proliferation and polarization (including type 1 T helper and IFN gamma-producing CD8+ T cells). Moreover, CDCP1, Hsp70, and Hsp90 also increased in RT-TDEs and may improve tumor immunogenicity. In addition, proliferation of natural killer (NK) cells was detected. On the other hand, radiation caused an increase in miR-378-3p and PD-L1, which reduced the secretion of granzyme-B and downregulated CD69 levels, respectively, thus inhibiting the cytotoxicity of NK cells and T cells, which eventually lead to tumor growth. *Abbreviations*: IFN = interferon; TNF = tumor necrosis factor; IL = interleukin.

molecules and proinflammatory cytokines (TNF-α and IL-12p70) in DCs, thus enhancing the immunocompetence and antigen-presenting ability of DCs and eventually promoting T cell proliferation and polarization (including type 1 T helper and IFN-γ−producing CD8 + T cells), as well as reduced tumor growth.

The effects of exosomes on NK cells were also studied. Jella et al[29] reported that exosomes derived from 10 Gy −irradiated melanoma cells showed significant local antitumor ability in vivo. The antitumor effect was correlated to a sharp increase in IFN-γ−producing NK cells. These results showed that irradiated cancer cells could activate DCs and NK cells, which eventually primed antitumor T cells, but the mechanisms needed further study. Another research found that the loading of miR-378-3p was increased in irradiated TDEs, which was due to TeT2-mediated demethylation of miR-378 promoter and overexpression of miR-378a-3p after irradiation, thereby decreasing the secretion of granzyme-B by NK cells and reducing NK cytotoxicity. This has also been found in human blood samples.[30] In addition, exosomes are capable of changing the proportions of immune cells, thus regulating the TME. An in vitro study on dose rate effect of stereotactic body RT for NSCLC found that both NK and B cell proportions in peripheral blood mononuclear cells were significantly higher after cocultured with 10 Gy −irradiated tumor cells and reached peaks in high-dose treatment groups. However, the proportion of CD3+ T cell subsets was not affected. These results indicated that high-dose-rate radiation-induced TDEs contributed to the polarization of B and NK cell subsets in peripheral blood mononuclear cells.[31] In general, TDEs were demonstrated to have a dual effect on tumor growth.

In adaptive immunity, T cells are the effector cells or targets for RT-associated exosomes, so their activation is pivotal in antitumor immune responses, which are largely correlated to DCs, and TDEs are an important part of this process. TDEs could trigger antitumor immunity against primary tumor and metastasis by enhancing CD8+ and CD4+ T cell infiltration via dsDNA and other molecules. Lin et al[28] studied the components of radiation-induced (8 Gy) TDEs, and they discovered that CUB domain−containing protein 1 (CDCP1) inside RT-TDEs, which were upregulated after radiation, could be regarded as tumor-associated antigens because they were widely expressed in various cancers and triggered antitumor immunity to inhibit both tumor growth and metastasis. Similarly, heat-shock proteins (mainly Hsp70 and Hsp90) also increased in RT-TDEs and may improve tumor immunogenicity. In other words, both tumor-associated antigens and HSPs encapsulated in RT-TDEs can modulate antigen-specific CD4+ and CD8+ T cell activation via DC cross-presentation pathways, while CD8+ T cells were activated through PI3K-Akt signaling, thus generating antitumor immune responses.

Although the induction of antitumor immunity by irradiated TDEs could represent an effective approach to suppress cancer progression, radiation is a double-edged sword to the immune system, considering its coexisting antitumor and immunosuppressive effect. With the results of the PACIFIC trial (NCT02125461),[32] RT is considered a promising combination therapy with immunotherapy, such as immune checkpoint inhibitors (ICIs), to enhance efficacy. ICIs are monoclonal antibodies designed to target negative regulatory pathways of T cells to promote an antitumor immune response.[33] Immune checkpoint molecules such as PD-L1 are shown on tumor cells and TDEs. A low dosage of radiation can increase the expression of certain immune checkpoint molecules such as PD-L1 on the surface of tumor cells, which downregulate CD69 levels, leading to the inactivation of cytotoxic T cells.[34] Clinical data showed that the upregulation of PD-L1 is common in TDEs, including triple-negative BC and head and neck squamous cell carcinomas (HNSCC), especially in patients treated with traditional clinical interventions, such as chemotherapy and RT.[34,35] In addition, fractionated RT delivered in combination with αPD-1 or αPD-L1 monoclonal antibodies generates effector CD8+ T cell responses that improve local tumor control and long-term survival.[36] Hence, many combination therapies have come into use or are under clinical trials, such as a phase II study that combined irradiated PD-L1 CAR-NK cells plus pembrolizumab plus N-803 for recurrent/metastatic gastric or head and neck cancer (NCT04847466) and our phase II study focusing on stereotactic body RT for oligoprogressive NSCLC after treatment with PD-1 ICIs (NCT04767009), etc.

While the primary focus of studies in this area has been on how radiation alters the cargo within exosomes, less attention has been given to the process of uptake itself or the underlying mechanisms. Existing research does indicate that radiation exposure tends to increase the uptake of exosomes by cells.[1] Changes in the levels or structures of proteins on exosomes or the cell membrane greatly affect how exosomes are recognized and absorbed.[37] Hazawa et al[38] found that radiation increased cellular uptake of exosomes through CD29/CD81 complex formation. Several studies have indicated that radiation impacts endocytosis by elevating the expression of dynamin 2 in recipient cells, which is associated with enhanced uptake of exosomes.[39,40] In general, radiation can increase the uptake of exosomes, but the specific mechanism is not well studied.

The effect of radiation on immune cell −derived exosomes

Immune cell−derived exosomes are also reported to convert the immune microenvironment and either facilitate or inhibit tumor development. When taking radiation into account, these effects can be reinforced or weakened via different components delivered by immune cell −derived exosomes.

Studies in this field mainly focus on exosomes derived from different subtypes of T cells Fig. 2. Min et al[41] found that exosomes derived from irradiated esophageal carcinoma−infiltrating T cells promoted epithelial-mesenchymal transition (an important process in esophageal cancer metastasis) in a radiation dose−dependent manner. The procedure may be regulated by β-catenin and the nuclear factor κB/Snail pathway in vitro. To be specific, nuclear factor κB was upregulated after being treated with irradiated exosomes, thus regulating Snail, which acts as a common downstream target of the epithelial-mesenchymal transition. β-Catenin facilitated cell adhesion and formed the transcription factor coactivation complex with T-cell factor (β-catenin/TCF/LEF complex, TCF, T-cell factor; LEF, lymphoid enhancing factor. In another research, Wang et al[42] investigated the function of exosomes derived from $\gamma\delta$-T cells ($\gamma\delta$-T-Exos) on RT and antitumor ability against nasopharyngeal carcinoma (NPC). They examined the interactions between NPC cells and $\gamma\delta$-T-Exos, as well as the combination of radiation and $\gamma\delta$-T-Exos. They revealed that $\gamma\delta$-T-Exos killed NPC cells by inducing cell apoptosis through Fas/FasL and DR5/TRAIL pathways, thus inhibiting tumor progression in vivo and extending the survival of tumor-bearing mice. Furthermore, $\gamma\delta$-T-Exos were found to facilitate T cell migration into TME via the CCR5 pathway, and the antitumor effect of T cells was preserved in the immunosuppressive microenvironment. When combining $\gamma\delta$-T-Exos with RT, a significantly higher rate of apoptosis was detected than monotherapy, and radioresistance of $CD44^{+/high}$ NPC cells (ie, NPC cancer stem-like cells) was overcome. These effects may be due to radiation causing tumor cells to phagocytose more exosomes. There are few relevant studies in this field, and further exploration is needed to uncover the role and mechanism of immune cell−derived exosomes in RT, thus guiding clinical practice.

It is worth noting that radiation can kill immune cells, which varies based on cell type and radiation dose. This could impact the release of exosomes, as immune cells are a source of these vesicles. Falcke et al[43] studied the radiosensitivity of human immune cells exposed to doses ranging from 0.01 to 60 Gy. They focused on how different radiation doses affected apoptosis, primary necrosis, and secondary necrosis in these cells. The findings revealed varying radiosensitivities among immune cells, with monocytes being the most resistant. T cells were moderately sensitive to radiation and mainly died from necrosis, whereas B and NK cells mainly died from apoptosis and were more sensitive. The study also observed the effects of low-dose RT (LDRT, 0.3-0.7 Gy) on immune cells, noting

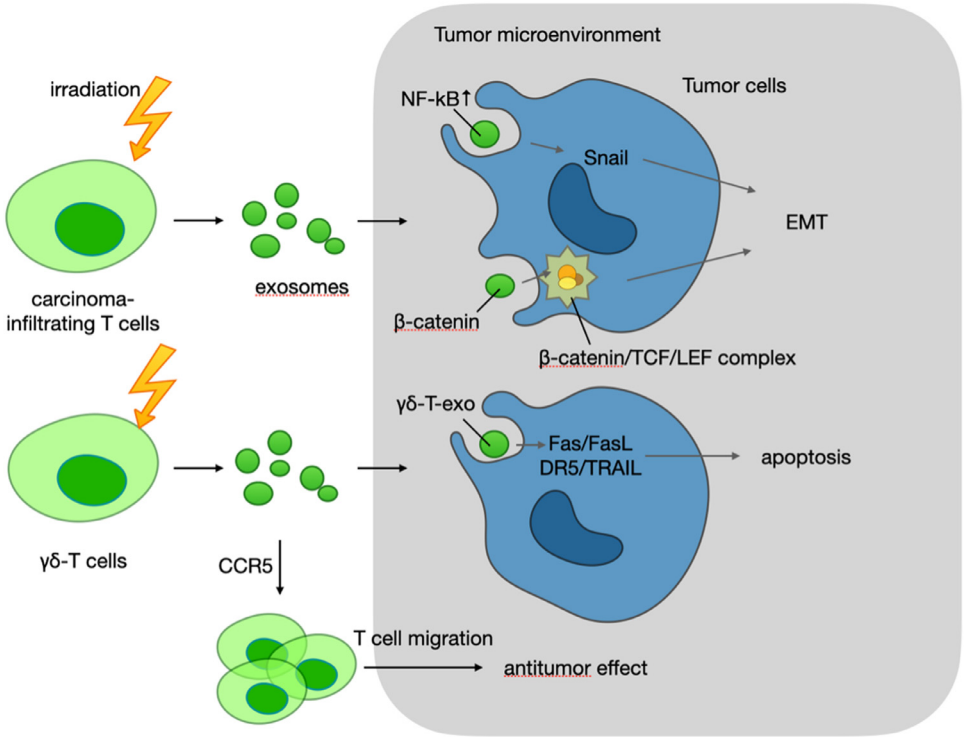

Figure 2 The effect of radiation on immune cell−derived exosomes. The figure focuses on 2 types of T cells: esophageal carcinoma−infiltrating T cells and $\gamma\delta$-T cells. Irradiated exosomes from esophageal carcinoma−infiltrating T cells promote epithelial-mesenchymal transition (EMT) through β-catenin and nuclear factor κB (NF-κB)/Snail pathways. Exosomes derived from $\gamma\delta$-T cells ($\gamma\delta$-T-exo) induced apoptosis through the Fas/FasL and DR5/TRAIL pathways, and facilitating T cell migration via the CCR5 pathway. *Abbreviations:* TCF = T-cell Factor, LEF= lymphoid enhancing factor.

that B and NK cells were more sensitive to LDRT, which might lead to attenuation of inflammation. This research provided a basis for optimizing RT and considering immunotherapy integration that immune cells differed in their radiosensitivity, with monocytes being the most radioresistant.

The Clinical Applications of Exosomes

Apart from the accelerating development of combining immunotherapy and RT in laboratories, some relevance also emerged in medical practice, where exosomes may play a pivotal role Fig. 3. Since the crosstalk of exosomes in TME can suppress differentiation, activation, and proliferation of immune cells and inhibit or promote tumor progression, it is reasonable to assume that they have some potential functions in RT. Owing to their long circulatory half-life, low toxicity, and compliance with modification, exosomes can be manufactured as delivery vehicles for nucleic acids, proteins, and antibodies among others.[44] On account of tumoral heterogeneity, traditional examinations are incapable of giving accurate results. However, the improvement in detection techniques has made liquid biopsy of exosomes feasible, providing a more accessible and specific method to identify cancer types, stratify patients, and predict outcomes noninvasively.

Exosomal trafficking during cancer development and progression can be used in cancer diagnosis, prognostication, and treatment strategies Table 1.[45] Several substances encapsulated in exosomes are reported to have a promising predictive effect, such as the downregulation of hsa-miR-126 and hsa-miR-183 in the serum of patients with stage IV NSCLC [46] and increased serum levels of exosomal miR-373 in receptor-negative breast tumors.[47] When it comes to immunotherapy plus RT, liquid biopsy of exosomes also performed well. The results of a phase I study of 18 patients with HNSCC who received a combination of cetuximab, ipilimumab, and intensity-modulated RT and were serially monitored for TDE and T cell −derived exosomes showed that total exosome proteins, TDE/total exosome ratios, total CD3+, CD3(−)PD-L1+, and CD3 + 15s+ (Treg-derived) exosomes were upregulated in patients whose disease recurred within 2 years.[48] In esophageal squamous cell carcinoma, studies have also shown that plasma exosomal miRNAs can predict therapeutic outcome relevant to RT, as well as their roles in the DNA damage process and endosomal-mediated transport. For example, it was demonstrated that miR-652 and

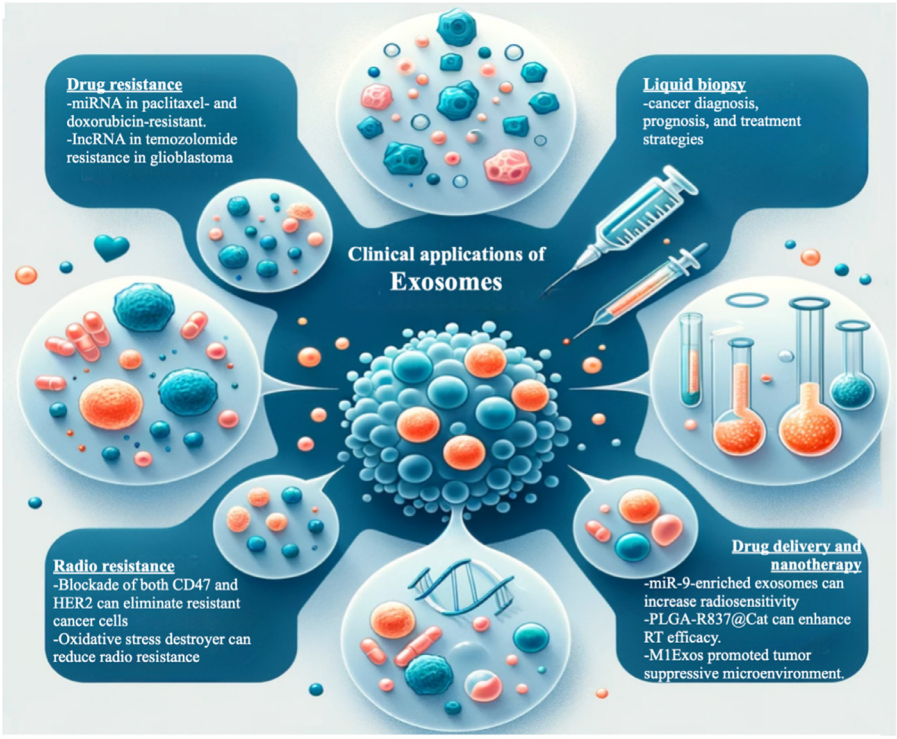

Figure 3 Clinical applications of exosomes. This figure highlights applications in liquid biopsy, immunotherapy, radiation therapy (RT), and drug delivery. It visually represents how exosomes facilitate the delivery of nucleic acids and proteins, contribute to liquid biopsy for cancer diagnosis, and play a dual role in affecting drug and radioresistance in cancer cells. Additionally, it depicts the potential of exosomes in nanomedicine, especially in enhancing RT and targeting tumor microenvironments.
Abbreviations: Cat = catalase; lncRNA = long noncoding RNA; miRNA = microRNA; PLGA = poly(lactic-co-glycolic) acid.

miR-30a alter migration but not proliferation.[49] These studies highlight the differentially expressed components of exosomes during and before RT and provide a reference for exploring noninvasive plasma biomarkers for diagnosis and evaluation of therapeutic effects.

Furthermore, exosomes are reported to either aggravate or eliminate drug resistance and radioresistance, providing promising targets for therapeutic use. For example, paclitaxel- and doxorubicin-resistant BC cells can transfer their chemoresistance through exosomal miR-100, miR-222, miR-30a, and miR-17.[50] By contrast, temozolomide resistance in glioblastoma could be reduced by exosome-mediated transfer of temozolomide-associated long noncoding RNA to microglial cells.[51] In terms of radioresistance, classic RT for mouse BC increases both CD47 and HER2 expression simultaneously, and upregulation of CD47 and HER2 is more frequently detected in patients with recurrent BC with poor prognosis, which is caused by CD47-mediated antiphagocytosis conjugated with HER2-prompted proliferation. Therefore, blocking CD47 or HER2 reduces both receptors with diminished clonogenicity and augmented macrophage phagocytosis. Hence, blockade of both CD47 and HER2 is suggested to eliminate resistant cancer cells in BC RT.[52] Considering the adverse effects of high-dose radiation, Huang et al. produced an oxidative stress destroyer to enhance LDRT. The destroyer can decrease the content of glutathione in the TME and catalyze H_2O_2 to produce a large amount of OH. The exosome membrane can render FeS_2 with admirable homologous targeting ability, and all these elements showed the ability to reduce radioresistance. Notably, no side effect was observed in vivo.[53] Although the mechanisms are gradually uncovered, most of the studies still lie in the laboratories. The clinical application of irradiated exosomes combining immune cells remains to be explored.

In addition to therapeutic and diagnostic functions, exosomes are glittering in drug delivery and nanomedicine. Nanotherapy refers to the use of nanoparticles at the nanoscale range for treating various diseases that offer improved drug stability and solubility and target human diseases with minimal side effects[26] In HNSCC, miR-9-enriched exosomes from human papilloma virus (HPV) + HNSCC can polarize macrophages into M1 phenotype and increase the radiosensitivity of HPV + HNSCC. Therefore, miR-9 may be used as a potential treatment for HNSCC.[54] Moreover, Chen et al[55]. fabricated a core−shell nanoparticles−based poly(lactic-co-glycolic) acid (PLGA) by encapsulating water-soluble catalase (Cat), an enzyme that can decompose H_2O_2 to

Table 1 Exosomes as biomarkers in clinical trials

Cancer type	Exosomal cargo	Function	Reference, year published
Breast cancer	Exosomal miR-328	High miR-328 levels suggested low intestinal breast cancer resistance protein activity, resulting in the high AUC of sulfasalazine.	Gotanda et al,[57] 2016
Lung adenocarcinomas	Exosomal EGFR	Exosomal EGFR levels may reflect changes in tumor EGFR expression in response to therapy.	Yu et al,[58] 2017
HCC	Exosomal miR-638	Patients with HCC with lower levels of serum exosomal miR-638 had larger tumor size, more vascular infiltration, advanced TNM stage, and poor OS.	Shi et al,[59] 2018
NSCLC	Exosomal lnc-SNAPC5-3:4	The upregulation of lnc-SNAPC5-3:4 suggested the efficacy of anlotinib.	Liu et al,[60] 2022
Ovarian cancer	PS-positive exosomes	PS-positive exosomes can distinguish between malignant and benign ovarian cancer, and a higher PS level indicates more malignant cancer.	Lea et al,[61] 2017
PA	CDK6, RHOU	Serum exosomal CDK6 and RHOU mRNA can be used to predict the invasiveness of NF-PAs. A combination of the 2 genes performs better in distinguishing invasive NF-PAs.	Yu et al,[62] 2019
Pancreatic cancer	Exosomal C133	Exosomal CD133 is positively correlated with better OS in patients with pancreatic cancer, which can be used as a prognostic biomarker.	Sakaue et al,[63] 2019
NSCLC	Exosomal miRNA-32	Plasma miRNA-32 levels were correlated with the efficacy of platinum-based chemotherapy and survival, which may be useful for predicting the effectiveness of platinum-based chemotherapy and prognosis in NSCLC.	Xu et al,[64] 2019

Abbreviations: AUC = area under curve; EGFR = epidermal growth factor receptor; CDK6 = cyclin-dependent kinase 6; HCC = hepatocellular carcinoma; mRNA; messenger RNA; miRNA = micro RNA; NF = nonfunctioning; NSCLC = non-small cell lung cancer; OS = overall survival; PA = pituitary adenoma; PS = phosphatidylserine; RHOU = ras homolog family member U.
This table summarizes the clinical trials related to exosome biomarkers, focusing on the role of exosomes in the diagnosis of tumors and the prediction of drug efficacy.

generate O_2, inside the inner core and loading hydrophobic imiquimod (R837), a Toll-like receptor 7 agonist, within the PLGA shell. The PLGA-R837@Cat nanoparticles were designed to relieve the tumor hypoxia and modulate the immune-suppressive TME by inducing antitumor response and inhibiting tumor metastases (together with Cytotoxic T-lymphocyte protein 4 inhibitor), thus enhancing RT efficacy. Moreover, a long-term immunologic memory effect to protect mice from tumor rechallenging is observed after such treatment. This nanoparticle offers a potential possibility of combining nanomedicine and RT.[55] Similarly, in order to enhance RT, Ma et al[56] engineered M1 macrophage–derived exosomes as effective RT sensitizers to polarize M2 macrophages into M1 phenotypes, as well as relieve tumor hypoxia, enhance DNA damage, inhibit DNA damage repair, and relieve the immunosuppression of T cells, together leading to the remodeling of the tumor suppressive microenvironment. Although still in its infancy, exosomes have a profound future in the field of nanomedicine, providing a more efficient and accurate administration route for cancer treatment.

Conclusions

This review systematically summarizes the regulatory role of exosomes derived from irradiated tumor cells and immune cells in TME. Past studies have shown that exosomes can regulate tumor growth, invasion, metastasis,

angiogenesis, and immunotherapy resistance. Both TDE and immune cell–derived exosomes participate in the intercellular communication in TME. It has been reported that exosomes carry and transfer various components, such as proteins, DNA, miRNAs, and long noncoding RNAs, leading to changes in the function and/or phenotype of recipient cells. When the factor of RT is added, these effects can be promoted or inhibited, thereby affecting tumor growth or metastasis. Understanding the correlation between RT, exosomes, and immune responses is essential to explore biomarkers for early detection, diagnosis, and prognosis of tumors and to design more effective antitumor immunotherapy. Besides, exosomes are emerging as novel methods for drug resistance and radioresistance, as well as drug delivery, which offer the possibility to optimize cancer treatment. However, the complexity and diversity of exosomes lead to different effects on the same recipient cell, and the role of exosomes in different TMEs is also different. There still exist many unsolved problems.

Disclosures

None.

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