细胞外囊泡在肿瘤放疗抵抗调控及增敏策略中的研究进展

刘　瑄[1,2]　官成浓[1,2]

[1]（广东医科大学附属东莞第一医院　东莞　523106）

[2]（广东医科大学　湛江　524023）

摘要　细胞外囊泡（Extracellular vesicles，EVs）在肿瘤放疗抵抗（Radiation resistance，RR）与增敏中具有双重作用。一方面，肿瘤来源EVs通过转运miRNA（如miR-1246、miR-21）、lncRNA（如NORAD）及蛋白质（如pATM、Survivin），调控DNA损伤修复、细胞周期和凋亡通路，促进RR形成；另一方面，EVs凭借天然纳米载体特性（生物相容性、靶向性及血脑屏障穿透能力），可作为放疗增敏剂的理想递送平台。工程化策略（如表面修饰、CRISPR/Cas9装载）可进一步提升EVs的靶向性与功能性。此外，EVs通过调控免疫微环境（如PD-L1转移、M2型巨噬细胞极化）影响放疗疗效，呈现“免疫激活”与“免疫抑制”的双刃效应。尽管EVs在个体化放疗增敏中潜力巨大，其临床转化仍面临规模化生产、标准化及安全性等挑战。本文系统综述EVs在肿瘤RR调控及增敏中的分子机制与应用进展，为优化放疗策略提供新思路。

关键词　细胞外囊泡，放疗抵抗，DNA损伤修复，放疗增敏

中图分类号　R730.55

DOI: 10.11889/j.1000-3436.2025-0061

CSTR: 32195.14.j.JRRRP.1000-3436.2025-0061

引用该文：

刘瑄, 官成浓. 细胞外囊泡在肿瘤放疗抵抗调控及增敏策略中的研究进展[J]. 辐射研究与辐射工艺学报, XXXX, **XX**(XX): XXXXXX. DOI: 10.11889/j.1000-3436.2025-0061.

LIU Xuan, GUAN Chengnong. Progress of extracellular vesicles in tumor radiotherapy resistance regulation and sensitization strategies[J]. Journal of Radiation Research and Radiation Processing, XXXX, **XX**(XX): XXXXXX. DOI: 10.11889/j.1000-3436.2025-0061.

基金资助：广东省基础与应用基础研究基金省市联合基金项目（2023A1515140082）、广东医科大学附属东莞第一医院第五批高层次人才科研资助计划资助项目（GCC2024006）；广东医科大学附属东莞第一医院“攀峰100”联合培优计划资助项目（PF100-1-07）

第一作者：刘瑄，女，2000年出生，医学硕士研究生在读，E-mail: 2467962149@qq.com

通信作者：官成浓，教授，博士研究生导师，E-mail: guanchengnong@gdmu.edu.cn

收稿日期：初稿 2025-07-16；修回 2025-09-05

Supported by the Provincial and Municipal Joint Fund of the Guangdong Basic and Applied Basic Research Foundation (2023A1515140082), the Fifth Batch of High-Level Talent Research Support Program of Dongguan First People's Hospital, Affiliated to Guangdong Medical University (GCC2024006), and the “Peak Climb 100” Joint Training Program of The First Dongguan Affiliated Hospital of Guangdong Medical University (PF100-1-07)

First author: LIU Xuan (female) was born in 2000, master of medicine candidate, E-mail: 2467962149@qq.com

Corresponding author: GUAN Chengnong, professor, doctoral supervisor, E-mail: guanchengnong@gdmu.edu.cn

Received 16 July 2025; accepted 05 September 2025

Progress of extracellular vesicles in tumor radiotherapy resistance regulation and sensitization strategies

LIU Xuan[1,2]　GUAN Chengnong[1,2]

[1](*The First Dongguan Affiliated Hospital of Guangdong Medical University*, *Dongguan 523106*, *China*)

[2](*Guangdong Medical University*, *Zhanjiang 524023*, *China*)

ABSTRACT　Extracellular vesicles (EVs) exert dual roles in tumor radiation resistance (RR) and radiosensitization. On one hand, tumor-derived EVs transport miRNAs (e.g., miR-1246, miR-21), long non-coding RNAs (e.g., NORAD), and proteins (e.g., pATM, Survivin) to regulate DNA damage repair, cell cycle, and apoptosis pathways, thereby promoting RR development. On the other hand, EVs, leveraging their inherent properties as nanocarriers (biocompatibility, targeting capabilities, and blood-brain barrier penetration), serve as an ideal delivery platform for radiosensitizers. Engineering strategies (e.g., surface modification, CRISPR/Cas9 loading) can further enhance EVs' targeting and functionality. Additionally, EVs influence radiotherapy efficacy by modulating the immune microenvironment (e.g., PD-L1 transfer, M2 macrophage polarization), exhibiting a double-edged effect of "immune activation" and "immune suppression." Despite their immense potential in personalized radiotherapy sensitization, clinical translation faces challenges including large-scale production, standardization, and safety. This systematic review summarizes the molecular mechanisms and application progress of EVs in regulating tumor response to radiotherapy and enhancing sensitivity, offering new insights for optimizing radiotherapy strategies.

KEYWORDS　Extracellular vesicles, Radioresistance, DNA damage repair, Radiosensitization

CLC　R730.55

全球癌症统计数据显示，2022年新发癌症病例达1 998万例，死亡约974万例[1]，恶性肿瘤仍是威胁人类健康的重大公共卫生问题。放射治疗（Radiotherapy，RT）与手术、化疗并列为肿瘤三大传统治疗方式[2]，约50%的肿瘤患者在治疗过程中需接受RT[3]。临床上，RT主要指外照射治疗（External beam radiotherapy，EBRT），即通过直线加速器产生的高能粒子束杀伤肿瘤细胞。放疗敏感性受肿瘤类型、分期、个体差异及照射剂量等多因素影响，部分患者会出现放疗抵抗（Radiation resistance，RR），导致复发风险增加及预后不良[4-5]。因此，深入阐明RR的分子机制并探索有效的放疗增敏策略，已成为当前肿瘤治疗研究的重要方向。

细胞外囊泡（Extracellular vesicles，EVs）是近年肿瘤微环境研究的热点，其直径为30~2 000 nm，能够携带蛋白质、核酸（miRNA、lncRNA、mRNA）、脂质及代谢物等[6]。作为细胞间通讯的重要介质，EVs在肿瘤发生发展、免疫逃逸及治疗耐受中发挥关键作用[7-8]。研究表明，EVs可通过调控DNA损伤修复、细胞周期进程及凋亡信号通路等机制参与RR形成[3,9]。另一方面，凭借低免疫原性、高稳定性及良好生物相容性[10]，EVs被认为是极具应用前景的放疗增敏药物递送平台。本文将系统综述EVs在RR机制及增敏策略中的作用，以期为优化肿瘤放疗方案提供新思路。

1　细胞外囊泡的生物学特性与分子功能

EVs是一类由细胞主动分泌、以磷脂双层膜包裹的纳米级囊泡[11]，广泛存在于血液、尿液、唾液等多种体液中[12-13]，能够稳定携带并转运多种生物活性物质[14]。根据其生物起源及形成方式，EVs主要分为3类：外泌体（Exosomes）、微囊泡（Microvesicles）和凋亡小体（Apoptotic bodies）。其中，外泌体直径一般为30~150 nm，主要由多泡体（Multivesicular bodies，MVBs）与细胞膜融合后释放至胞外，是当前研究最为深入的一类EVs，参与多种生理与病理过程[15]；微囊泡的直径范围较宽（50~1 000 nm），主要由细胞膜直接外翻形成；凋亡小体则由发生程序性死亡的细胞断裂产生，直径可达1~5 μm[16-18]。尽管三者在形成机制、结构及功能上存在差异，当前研究通常将其统称为EVs[19]（图1）。

在肿瘤微环境中，肿瘤来源的EVs（tumor-derived EVs，TEVs）可通过转运miRNA、lncRNA、蛋白质等信号分子，重塑免疫微环境、促进血管生成

和上皮-间质转化（Epithelial – mesenchymal transition，EMT），从而增强肿瘤细胞存活能力[20-21]。此外，EVs具备膜受体靶向性、低免疫原性和高稳定性[22]，因此，成为理想的药物递送载体，为放疗增敏策略提供了天然优势（图2）。

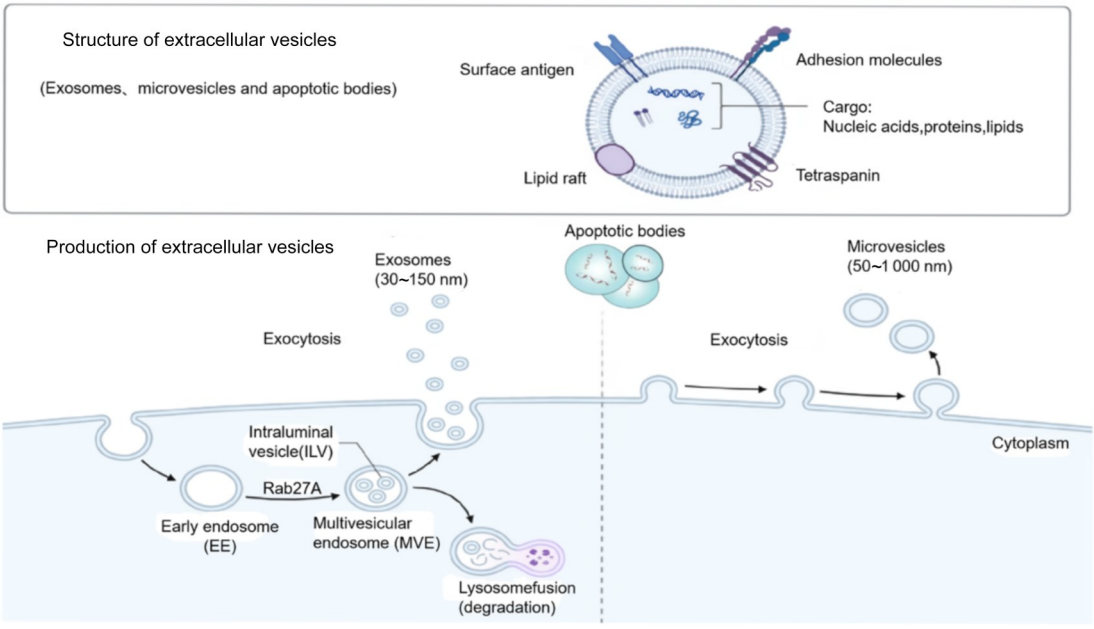

图1 细胞外囊泡的结构与产生过程。EVs主要包括外泌体、微泡和凋亡小体，其生物发生途径和特征各不相同

Fig.1 Structure and biogenesis of extracellular vesicles. EVs mainly include exosomes, microvesicles, and apoptotic bodies, which differ in biogenesis pathways and characteristics

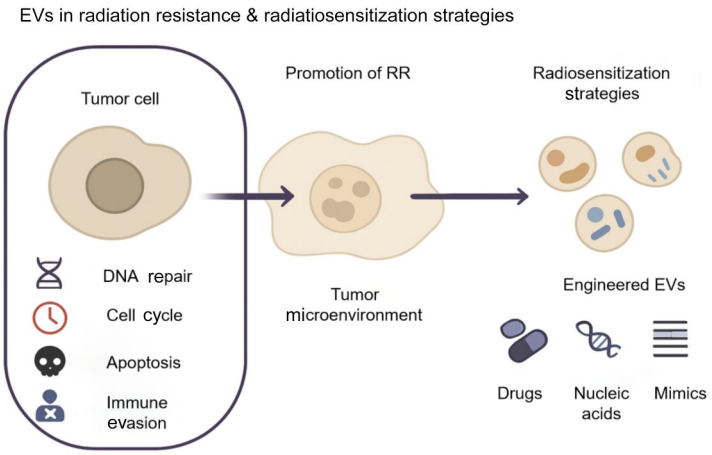

图2 细胞外囊泡在肿瘤放疗抵抗与增敏中的双重作用示意图。EVs可通过调控DNA修复、细胞周期、凋亡及免疫反应等途径促进放疗抵抗；同时，工程化EVs亦可作为递送载体，实现放疗增敏，体现其“双刃剑”作用

Fig.2 Schematic illustration of the dual roles of extracellular vesicles in tumor radioresistance and radiosensitization. EVs contribute to radioresistance by modulating DNA repair, cell cycle, apoptosis, and immune responses, while engineered EVs can serve as delivery vehicles to enhance radiosensitivity, highlighting their "double-edged sword" role

2 细胞外囊泡在肿瘤放疗抵抗中的作用机制

RT主要通过诱导DNA损伤、阻滞细胞周期及激活凋亡通路来杀伤肿瘤细胞，但其疗效常受限于固有或获得性RR[23]。EVs作为微环境信息传递的核心介质，可通过运载多种信号分子参与RR形成。

值得注意的是，EVs中miRNA、lncRNA及蛋白质在结构修饰、包装方式及胞外稳定性方面与细胞内同类分子存在差异[24]。核酸可通过化学修饰或与RNA结合蛋白（RNA-binding proteins，RBPs）形成复合物，从而提升稳定性并增强受体细胞功能活性。例如，tRNA的D-loop修饰、hnRNPA2B1的

sumoylation及YBX1/La蛋白复合物均参与选择性装载和保护[25-27]

EVs的cargo封装是高度调控的主动过程：RBPs可识别特定序列基序（如hnRNPA2B1识别EXOmotifs GGAG、La识别miR-122的3'UUU与5'UGGA），膜蛋白（如CD63、CD9、Rab27a）则调控分泌与装载[25-27]。这些精细的RNA-蛋白互作机制不仅解释了货物的选择性富集，也体现了部分miRNA、lncRNA及蛋白质对EVs的高亲和性，从而实现了稳定递送和功能发挥。这为EVs在DNA损伤修复、细胞周期调控及凋亡抑制中的作用奠定了分子基础。

2.1 调控DNA损伤修复通路

DNA双链断裂（Double-strand break，DSB）是RT诱导细胞死亡的核心机制，DNA损伤修复能力直接决定肿瘤细胞对放疗的敏感性[28]。EVs可通过以下两种模式增强修复。

2.1.1 蛋白介导的修复通路激活

EVs可携带DNA修复相关蛋白或其调控因子，激活受体细胞中的DNA损伤应答（DNA damage response，DDR），促进非同源末端连接（Non-homologous end joining，NHEJ）或同源重组（Homologous recombination，HR）等修复机制，从而加快辐射诱导的DNA断裂修复[29-30]。例如，辐射处理的神经母细胞瘤SH-SY5Y细胞释放的EVs中，p53、pATM（磷酸化共济失调毛细血管扩张突变蛋白）及BRCA1（乳腺癌1号基因）表达显著上调，可促进受体细胞DSB修复，减少DNA损伤的积累[31]。进一步研究表明，这些EVs不仅增强DDR关键蛋白的表达，还可被非照射细胞摄取并激活AKT信号通路，从而诱导下游抗凋亡反应与迁移能力的增强，并促进上皮-间质转化（Epithelial-mesenchymal transition，EMT），共同增强细胞的放射存活能力。此外，在胶质母细胞瘤中，EVs还能转运DNA修复酶的转录物，如烷基嘌呤-DNA-N-糖基化酶（APNG）和O6-甲基鸟嘌呤-DNA甲基转移酶（MGMT），进一步提升肿瘤细胞对放疗的耐受性[32]。

2.1.2 非编码RNA介导的修复调控

EVs中的非编码RNA（如miRNA、lncRNA）可通过靶向DNA修复相关分子间接调控修复效率。例如，乳腺癌细胞释放的EVs能够改变DNA修复蛋白的磷酸化状态[33]，从而影响其修复效率。在食管鳞状癌细胞中研究发现，长链非编码RNA NORAD（非编码RNA激活剂）下调后，可促进miR-199a-5p封装至EVs，后者通过靶向EEPD1（DNA修复蛋白）抑制ATR/Chk1信号通路，最终增强DNA修复和RR[34]。

2.2 重塑细胞周期分布

肿瘤细胞在不同周期阶段对放疗的敏感性显著不同（G2/M期最敏感，G1期较低，S期最低）[35-36]。EVs通过调控周期关键节点，促使肿瘤细胞从敏感时相逃逸至抵抗时相，从而削弱放疗杀伤作用[37]。

2.2.1 非编码RNA主导的周期时相调控

EVs携带的miRNA可直接靶向周期调控因子。例如：在胰腺癌中，放射损伤后的肿瘤细胞释放EVs，富集miR-194-5p，可诱导G1/S期阻滞并促进DNA损伤修复，从而增强放疗耐受性[38]。在缺氧性结直肠癌（CRC）中，EVs中miR-663a表达水平显著下降，削弱了其对TGF-β1的负向调控能力，导致TGF-β1表达上升、EMT激活及Cyclin E表达恢复，使细胞周期由G1期向S期推进，最终降低放疗敏感性[36,39]。

2.2.2 功能蛋白的间接调控作用

尽管尚缺乏直接证据表明周期抑制蛋白（如p21、p27）能通过EVs传递，但其上游信号通路的调控可能是潜在机制。例如，HSP90可与CDK4（周期蛋白D1的伴侣激酶）结合，维持其活性构象，从而促进Cyclin D1/CDK4复合物的功能[40]。尽管该研究未直接证明HSP90通过EVs递送，但其提示EVs可能通过携带HSPs等分子伴侣，间接影响周期相关蛋白的稳定性，进而调控细胞周期进程。

2.3 抑制凋亡并激活存活信号

细胞凋亡是放疗诱导肿瘤细胞死亡的重要机制之一，也是决定治疗反应的关键环节[41]。EVs可通过运载抗凋亡或促凋亡分子，直接或间接调控凋亡信号通路，从而影响放疗敏感性[42]。

2.3.1 抗凋亡蛋白介导的直接抑制

EVs可携带Bcl-2、Bcl-xL等抗凋亡蛋白，通过抑制促凋亡因子Bax的活性，维持线粒体膜的完整性，从而阻止细胞凋亡的启动[43]。此外，RT后，肿瘤细胞释放的EVs中Survivin（一种凋亡抑制蛋白）的水平显著升高。Survivin通过负性调控细胞凋亡信号通路，削弱了RT诱导的细胞毒作用，进而增强肿瘤细胞的存活能力[43-44]。

2.3.2 非编码RNA的双向调控

EVs中的miRNA在凋亡调控中具有双重作用。一方面，在放疗后，EVs携带的某些miRNA（如miR-208a）可通过下调促凋亡蛋白（如PARP1、Bax）并上调Bcl-2等抗凋亡蛋白，降低肿瘤细胞的凋亡水平，增强其对放疗的抵抗能力[45]；另一方面，也有部分miRNA具有促凋亡效应，例如miR-22通过上调Bax、下调Bcl-2表达，增强细胞对放射损伤的敏感性[46]。此外，受照射的肿瘤细胞衍生的EVs通过转移miR-208a或miR-1246促进受体细胞的放射抗性，从而促进肺癌中的细胞增殖[45,47]。

综上所述，EVs通过调控DNA损伤修复、细胞周期分布和凋亡水平，在RR形成中发挥核心作用。除了上述机制，肿瘤免疫微环境的重塑也是RR的重要环节，相关内容将在§3.3中进一步阐述（图3）。

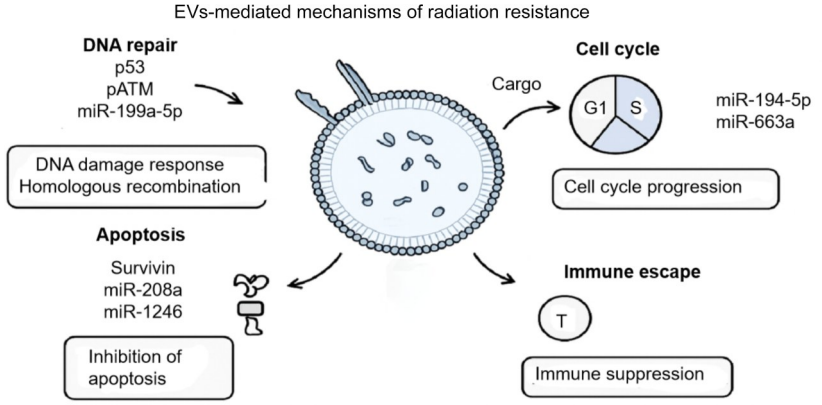

图3 细胞外囊泡介导的肿瘤放疗抵抗机制示意图。EVs通过运载特定核酸和蛋白质，促进DNA修复、调控细胞周期、抑制凋亡并介导免疫逃逸，从而削弱放疗效应

Fig.3 Molecular mechanisms of extracellular vesicle–mediated tumor radioresistance. EVs promote radioresistance by delivering specific nucleic acids and proteins that enhance DNA repair, regulate the cell cycle, inhibit apoptosis, and facilitate immune evasion, collectively reducing the efficacy of radiotherapy

2.4 不同肿瘤来源EVs在放疗抵抗机制中的差异

不同肿瘤来源的EVs在Cargo组成、信号通路调控及放疗敏感性方面存在显著差异（表1）。以非小细胞肺癌（NSCLC）、结直肠癌（CRC）和胶质瘤（GBM）为例，其EVs在分子运载特征与RR机制上呈现肿瘤特异性。

2.4.1 非小细胞肺癌（NSCLC）

放疗后NSCLC细胞释放的EVs主要表现为：（1）凋亡抑制：EVs富集miR-1246，可直接靶向死亡受体DR5，阻断外源性凋亡信号，从而增强放疗耐受性。临床检测亦发现，NSCLC患者血浆EVs中miR-1246水平显著升高，尤其在RR者中更为突出，提示其有望作为预测放疗响应的生物标志物[9,48]。（2）免疫抑制：EVs可转运PD-L1，与$CD8^+$T细胞表面PD-1结合，下调PI3K/AKT通路并诱导T细胞功能耗竭。最新研究显示，调控LAMTOR1-HRS轴可促进PD-L1溶酶体降解，减少EV-PD-L1释放并增强T细胞浸润，为放疗增敏提供潜在靶点[49-50]。

2.4.2 结直肠癌（CRC）

CRC基质细胞，尤其是癌症相关成纤维细胞（Cancer-associated fibroblasts，CAFs），衍生的EVs在TGF-β信号激活和细胞周期调控中作用显著：（1）CAF-EVs富集miR-93-5p，可下调FOXA1并解除其对TGFB3的抑制，从而驱动TGF-β活化并诱导放疗耐受。（2）CRC肿瘤细胞来源EVs（TEVs）亦可通过转运miR-590-3p激活PI3K/AKT通路，促进细胞存活与抵抗[51-52]。整体上，CRC-EVs更偏向于通过“细胞周期重塑+EMT/TGF-β激活”机制削弱放疗敏感性。

2.4.3 胶质瘤（GBM）

GBM来源EVs主要通过双重机制促进RR：（1）DNA损伤修复增强：GBM细胞中RAD51、Ku70/Ku80等DNA修复因子活性上调与RR密切相关。近期研究表明，EV-ncRNA可参与DDR关键节点调控，从而增强DNA修复能力、降低放疗敏感性。（2）免疫抑制微环境：胶质瘤干细胞（Glioma stem cells，GSC）释放的EVs富集miR-21等，可诱导巨噬细胞向M2样极化，形成免疫抑制微环境并削弱放疗效应[9,14,53]。

2.4.4 小结

不同肿瘤来源的EVs在RR机制上各具特征（表2）。NSCLC-EVs：以凋亡抑制与免疫逃逸为主；CRC-EVs：以细胞周期重塑与TGF-β/EMT激活为主；GBM-EVs：以DNA修复增强和免疫抑制为主。这些差异提示，未来应针对不同肿瘤类型设计分型化的放疗增敏策略。例如，靶向EV-PD-L1阻断免疫逃逸、抑制CAF-EVs的miR-93-5p-FOXA1-TGFB3轴，或干预GBM-EV介导的DDR-ncRNA网络，均有望提升放疗疗效和精准性。

表1 EVs携带关键cargo及其在放疗抵抗中的作用机制总结
Table 1 Summary of key cargo transported by EVs and their mechanisms in radiotherapy resistance

Cargo类型 Cargo Type	代表分子 Representative molecule	靶点/作用通路 Target/signaling pathway	功能结果 Functional outcome	癌种示例 Cancer type example
miRNA	miR-1246	靶向DR5（死亡受体5），抑制凋亡通路 Targeting DR5 (Death Receptor 5), inhibiting apoptosis pathways	抑制细胞凋亡，增强放射存活 Suppresses cell apoptosis, enhances radiation survival	非小细胞肺癌 Non-small cell lung cancer (NSCLC)
miRNA	miR-21	驱动M2型极化 Drives M2 polarization	抑制免疫微环境，削弱放疗效应 Suppresses immune microenvironment, weakens radiotherapy effects	胶质母细胞瘤 Glioblastoma (GBM)
miRNA	miR-208a	靶向p21和AKT/mTOR通路 Targeting p21 and AKT/mTOR pathways	促进肺癌细胞增殖，减少细胞凋亡 Promotes lung cancer cell proliferation, reduces apoptosis	肺癌 Lung cancer
miRNA	miR-199a-5p	靶向EEPD1 Targeting EEPD1	激活DNA损伤修复 Activates DNA damage repair	食管鳞癌Esophageal squamous cell carcinoma (ESCC)
lncRNA	H19	抑制p53通路 Inhibition of p53 pathway	减少细胞凋亡 Reduction of apoptosis	/
蛋白质 Protein	pATM	激活DNA损伤应答DDR通路 Activation of DNA damage response (DDR) pathway	加速DSB修复 Acceleration of DSB repair	神经母细胞瘤 Neuroblastoma
蛋白质 Protein	MGMT/APNG	修复烷基化DNA损伤 Repair of alkylated DNA damage	诱导放疗耐受 Induction of radiation resistance	胶质母细胞瘤 Glioblastoma (GBM)

表2 不同肿瘤来源EVs在放疗抵抗机制中的差异
Table 2 Differences in mechanisms of radiotherapy resistance among EVs from different tumor origins

肿瘤类型 Cancer type	代表性EVs cargo Representative EVs cargo	主要机制 Main mechanism	参考文献 References
非小细胞肺癌 NSCLC	miR-1246, EV-PD-L1	抑制凋亡（靶向DR5）、免疫逃逸（PD-L1/PD-1轴） Inhibits apoptosis (targeting DR5), immune evasion (PD-L1/PD-1 axis)	[9,48−50]
结直肠癌 CRC	miR-93-5p, miR-590-3p	激活TGF-β/EMT通路，重塑细胞周期 Activates TGF-β/EMT pathway, reshapes cell cycle	[51,52]
胶质母细胞瘤 GBM	miR-21, RAD51, Ku70/80	增强DNA修复能力、驱动M2型极化 Enhances DNA repair capacity, drives M2 polarization	[9,14,53]

3 细胞外囊泡作为放疗增敏剂的研究进展

除在RR形成中发挥作用外，EVs因其高生物相容性、低免疫原性和天然靶向能力，逐渐成为放疗增敏的新型递送平台[54−55]。

3.1 基于EVs的核酸/药物递送策略

作为天然纳米载体，EVs可靶向递送核酸类分子或小分子药物，调控放疗耐受相关通路，从而增强肿瘤细胞的放疗敏感性。已有研究证实，不同来

源的EVs，尤其是来自间充质干细胞（Mesenchymal stem cells，MSCs）或肿瘤相关细胞来源的EVs，在调控肿瘤放疗反应中发挥重要作用。例如，CAF-EVs富含miR-93-5p，可激活结肠癌TGF-β通路，促进放疗耐受[56]。类似地，Wan等[57]的研究表明，通过MSC-EVs递送miR-34c，能够有效抑制鼻咽癌细胞的增殖、迁移及其对放疗的耐受性。此外，有研究提出，局部放疗联合MSC-EVs递送的治疗策略，该策略不仅能够诱导癌细胞发生凋亡，还可能通过MSC-EVs所携带的特定信号分子作为“化学信号”，增强放疗敏感性并激活全身抗肿瘤免疫[58]。

综上所述，基于EVs的药物递送策略有望成为突破放疗抗性的重要方向。

3.2 工程化EVs增强靶向性和功能性

为进一步提升EVs在放疗增敏中的应用效率，研究者已开发出多种工程化策略，包括表面修饰、基因工程改造及融合脂质体技术[59]。工程化手段为EVs的放疗增敏应用提供了更大的可塑性。利用基因工程或化学修饰方法，可在EVs表面展示肿瘤靶向配体（如RGD肽、抗体片段等），显著增强其在肿瘤组织中的富集能力，从而提高局部药物浓度和放疗增敏效果[60]。同时，融合信号肽或穿膜蛋白（如Lamp2b、CD63）等分子，也被证实可增强EVs的组织特异性转运与胞吞效率[14,61]。

近年来，更前沿的研究已将CRISPR/Cas9系统封装进EVs中，实现功能性基因编辑。例如，通过EVs递送CRISPR/Cas9系统敲低KRAS突变型NSCLC细胞中的FAK基因，可诱导明显的DNA损伤并增强其对放疗的敏感性[62]。这类工程化EVs的策略不仅提供了多维度的放疗增敏机制，也为精准个体化治疗提供了新工具（表3）。

表3 工程化EVs增敏放疗的策略对比

Table 3 Comparison of strategies for radiotherapy sensitization using engineered EVs

工程化策略 Engineering strategy	技术手段 Technical approach	优点 Advantages	局限性 Limitations
表面修饰 Surface modification	化学偶联、脂质插层、配体修饰 Chemical conjugation, lipid insertion, ligand modification	提高肿瘤靶向性；可与放疗靶点结合 Enhances tumor targeting; enables binding with radiotherapy targets	修饰过程复杂，可能影响EVs稳定性 Complex process, may affect EV stability
基因编辑 Genetic engineering	在供体细胞中过表达特定miRNA/蛋白 Overexpression of specific miRNA/protein in donor cells	cargo来源稳定，可大规模制备 Stable cargo source, scalable production	基因修饰存在安全隐患 Potential biosafety concerns
药物负载 Drug loading	电穿孔、超声、冻融、共孵育 Electroporation, ultrasound, freeze-thaw, co-incubation	可实现化疗/放疗药物联合 Enables chemo-/radio-sensitizer co-delivery	装载效率有限，部分方法损伤EVs Limited loading efficiency; some methods damage EVs
材料融合 Material hybridization	与纳米颗粒/水凝胶结合 Hybridization with nanoparticles/hydrogels	改善EVs稳定性，延长体内半衰期 Improves EV stability, prolongs half-life in vivo	工艺复杂，临床转化难度高 Complex process, challenging clinical translation
人工EVs Artificial EVs	利用膜组装或仿生方法制备 Membrane assembly or biomimetic fabrication	可控性高，规模化生产潜力大 High controllability, scalable production potential	与天然EVs差异仍需评估 Differences from natural EVs require further evaluation

3.3 EVs介导免疫微环境重塑

放疗不仅可直接杀伤肿瘤细胞，还能通过释放肿瘤相关抗原和损伤相关分子模式（DAMPs）激活免疫反应[63]。然而，TEVs在辐射应激下的分泌量和cargo组成发生显著变化，既可能增强抗肿瘤免疫，也可促进放疗抵抗[64-65]（图4）。根据作用细胞类型和免疫反应阶段，其影响可分为固有性免疫与适应性免疫两类。

3.3.1 固有性免疫

（1）树突状细胞（DCs）。辐射后，TEVs富集核

酸（如 dsDNA、cGAMP）和 DAMPs，可通过 cGAS-STING 或 TLR 信号激活 DCs，促进抗原交叉递呈及 I 型干扰素产生，从而增强放疗的免疫增敏效应[66-67]。然而，部分 TEVs 携带 Trex1、caspase 3/9 等分子，或通过招募 MDSCs/Tregs 分泌 IL-10、TGF-β，可抑制 DC 成熟或下调 MHC 表达，削弱抗原呈递功能，形成免疫耐受[66-68]。值得注意的是，肿瘤来源的 cGAMP 亦可经 EVs 转运至 DCs，放大 STING 信号，这一通路在放疗-免疫协同中尤为关键[66,68-69]。

（2）巨噬细胞（TAMs）。TEVs 富含 miR-21、miR-1246 等 cargo，可驱动 TAM 向 M2 免疫抑制表型极化，经 STAT3/PI3K-AKT 等通路分泌 IL-10、TGF-β，从而营造免疫抑制与促血管生成的微环境[70-71]。尽管这些研究多基于非放疗模型，但考虑到放疗能够显著改变 TEVs 的分泌量与分子谱，其在放疗后驱动 TAM 极化、削弱免疫依赖性抗肿瘤效应的可能性值得关注。目前，放疗-TEVs-TAM 之间的直接机制证据仍有限，有待进一步研究。

（3）中性粒细胞。TEVs 可促进 N2 型免抑中性粒细胞分化并诱导 NETs 形成，通过释放蛋白酶和细胞因子抑制 T 细胞功能、促进转移[72-73]；辐射应激可进一步上调 CXCL-趋化轴及相关 cargo，加剧免疫抑制[74]。

（4）自然杀伤（NK）细胞。部分 TEVs 在表面呈递 NKG2D 配体或携带 TGF-β 及抑制性 miRNAs（如 miR-23a），可导致 NK 细胞 NKG2D 下调及去颗粒功能受阻，削弱其细胞毒活性[75-76]。尽管目前尚缺乏直接证据表明这一过程与放疗诱导的 NK 激活存在拮抗，但该机制提示 TEVs 可能在一定程度上限制放疗依赖的 NK 介导抗肿瘤效应。

（5）髓源抑制细胞（MDSCs）。TEVs 可通过携带 PD-L1、TGF-β 及 miRNAs（如 miR-21/miR-155 等）促进 MDSC 的扩增与免疫抑制功能，并抑制 DC 成熟与抗原递呈，从而削弱抗肿瘤免疫[76-77]。放疗诱导的炎症反应与 CCL2/CCR2 等趋化轴上调进一步增强 MDSC 的募集与活化[64]。

3.3.2 适应性免疫

（1）$CD8^+$效应 T 细胞与 $CD4^+$ T/Treg。放疗可诱导 TEVs 中 PD-L1 的上调，通过直接结合 $CD8^+$T 细胞表面受体，抑制其细胞毒活性（如降低颗粒酶 B 分泌、下调 CD69 表达），从而抵消放疗诱导的免疫原性效应[78]。临床观察亦发现，头颈部鳞状细胞癌与三阴性乳腺癌患者在放疗后循环 EVs 中 PD-L1 水平升高，与复发及预后不良相关，提示循环 EVs 中 PD-L1 可作为反映 RR 风险的潜在生物标志物[78]。相对地，DC-EVs 可移交抗原-MHC 复合物，增强交叉呈递与 $CD8^+$T 细胞激活，体现其免疫促进效应。此外，TEVs 携带的 TGF-β、IL-10 及 miRNAs（如 miR-214/miR-208b）能促进 Treg 扩增并抑制 Th1/Th17 极化，进一步削弱放疗后的抗肿瘤免疫反应[79-81]。

（2）B 细胞与调节性 B 细胞（Bregs）。TEVs 可诱导 Bregs 分泌 IL-10，间接抑制 $CD8^+$T 与 DC 活性[82]。放射应激会改变 TEVs 的释放量及 cargo，这一过程可能进一步影响 B 细胞介导的体液免疫和远处抗肿瘤效应，但关于“放疗直接重塑 B 细胞抗体谱”的证据仍有限，仍需深入研究[78]。

3.3.3 小结与策略启示

TEVs 在放疗后表现出双刃剑效应：一方面通过 dsDNA-cGAS-STING 及抗原递呈促进免疫活化，另一方面，通过 PD-L1 转移、M2/MDSC/Treg 极化及 NK 去活化抑制免疫，从而驱动 RR。潜在干预策略包括：（1）工程化 EVs 递送 STING 激动剂、siPD-L1 或免疫激活性 miRNA，放大抗肿瘤免疫链路并减弱免疫抑制[83]；（2）监测循环 EVs cargo（如 PD-L1、miR-21/miR-1246）预测放疗联合免疫疗法反应与耐受风险；（3）抑制肿瘤 nSMase2/Rab 通路减少免疫抑制性 TEVs 释放或利用 DC-EVs、NK-EVs 等“有益 EVs”实现免疫激活替代递送。

3.4 临床转化前景与挑战

EVs 及其工程化衍生物凭借天然生物相容性、低免疫原性及靶向递送能力[10]，已成为肿瘤治疗领域的新型载药系统。

3.4.1 多模态药物递送优势

天然 EVs 可高效负载化学药物（如阿霉素、顺铂）、核酸（siRNA/miRNA）及天然化合物（姜黄素），并通过细胞来源特性实现靶向富集。例如，牛奶 EVs 递送顺铂可逆转卵巢癌耐药性[84]，而工程化修饰（如 HER2 affibody 表面展示）进一步提升肿瘤靶向性。近期研究表明，EVs-脂质体融合颗粒通过共递送阿霉素与 GM-CSF，在腹膜癌模型中实现化疗-免疫协同效应，为联合治疗提供新思路[85]。

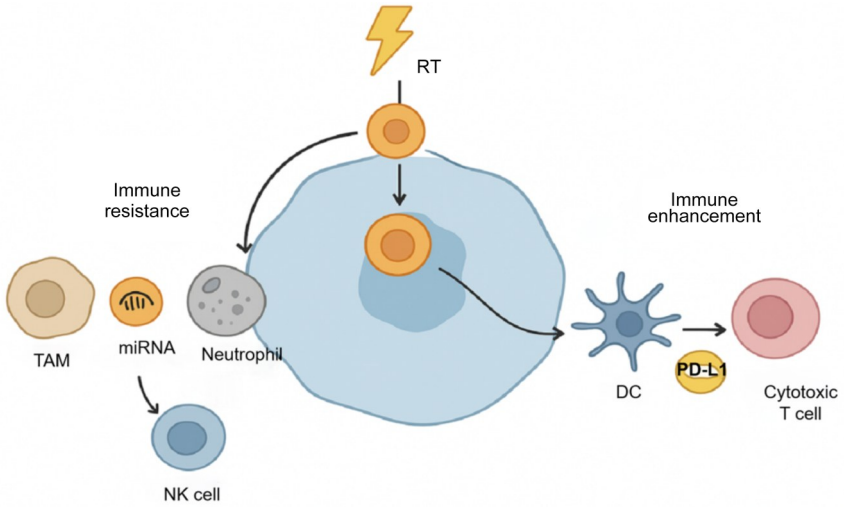

图4 放疗-EVs-免疫双刃效应机制示意图。放疗可改变肿瘤细胞EVs的分泌及cargo组成，EVs一方面通过调控免疫细胞功能促进免疫抑制，另一方面可激活抗原递呈与效应T细胞反应，增强抗肿瘤免疫，体现其“双刃剑”作用

Fig.4 Schematic illustration of the double-edged immunomodulatory effects of radiotherapy-induced EVs. Radiotherapy alters the secretion and cargo composition of tumor-derived EVs, which can either suppress antitumor immunity by modulating immune cell functions or enhance immune responses through antigen presentation and T cell activation

3.4.2 临床转化进展

目前，全球已有多项EVs载药研究进入临床阶段（表4）。例如，靶向KRAS G12D突变的siRNA-EVs[NCT03608631]在胰腺癌患者中显示出可控的安全性；植物源姜黄素EVs[NCT01294072]则验证了口服递送的可行性。这些研究为EVs从实验室走向临床奠定了基础。

表4 EVs及工程化衍生物在肿瘤载药中的临床前与临床研究实例

Table 4 Preclinical and clinical research examples of EVs and engineered derivatives in tumor drug delivery

类型 Type	载药物/cargo	靶向/功能 Target/Function	模型/受试者 Model/Subjects	研究阶段 Research Stage	PMID/NCT编号 PMID/NCT ID
化学药物 Chemotherapeutics	阿霉素 Doxorubicin	HEK293细胞来源增强肿瘤选择性 HEK293-derived, enhanced tumor selectivity	体外：SKBR-3/BT20细胞；体内：NA *In vitro*: SKBR-3/BT20 cells; *in vivo*: NA	临床前 Preclinical	30925190
化学药物 Chemotherapeutics	紫杉醇 Paclitaxel	巨噬细胞来源克服多药耐药 Macrophage-derived, overcoming multidrug resistance	体外：MDCKMDR1细胞；体内：Lewis肺癌转移模型 *In vitro*: MDCKMDR1 cells; *in vivo*: Lewis lung cancer metastasis model	临床前 Preclinical	26586551
化学药物 Chemotherapeutics	顺铂 Cisplatin	牛奶EVs逆转卵巢癌耐药 Milk-derived EVs, reversing ovarian cancer resistance	体外：A2780CP细胞；体内：卵巢癌异种移植模型 *In vitro*: A2780CP cells; *in vivo*: ovarian cancer xenograft model	临床前 Preclinical	35592860
siRNA	KRAS G12D siRNA	靶向突变基因沉默 Targeting mutant gene silencing	临床：转移性胰腺癌患者 Clinical: metastatic pancreatic cancer patients	临床 Clinical	NCT03608631

续表

类型 Type	载药物/cargo	靶向/功能 Target/Function	模型/受试者 Model/Subjects	研究阶段 Research Stage	PMID/NCT编号 PMID/NCT ID
miRNA	miR126	抑制PTEN/PI3K通路 Inhibition of PTEN/PI3K pathway	体外：A549细胞； 体内：肺癌异种移植模型 *In vitro*: A549 cells; *in vivo*: lung cancer xenograft model	临床前 Preclinical	31833519
天然化合物 Natural compounds	姜黄素 Curcumin	植物EVs口服递送 Plant-derived EVs, oral delivery	临床：正常及结肠癌患者 Clinical: healthy and colorectal cancer patients	临床 Clinical	NCT01294072
工程化EV Engineered EVs	EVs-脂质体融合颗粒 EV-liposome hybrid particles	共递送阿霉素/GM-CSF Co-delivery of doxorubicin and GM-CSF	体内：转移性腹膜癌模型 *In vivo*: metastatic peritoneal carcinoma model	临床前 Preclinical	32999828

注：PMID可在PubMed查询，NCT编号可在ClinicalTrials.gov查询相关临床试验信息。

Note: PMIDs can be searched on PubMed, and NCT numbers can be used to find related clinical trial information on ClinicalTrials.gov.

3.4.3 核心挑战与突破方向

尽管前景广阔，EVs载药系统仍面临着瓶颈：（1）规模化生产与标准化不足[86]；（2）药物装载与递送效率有限[87]；（3）体内分布与长期安全性不明[87-88]；（4）监管与质量控制体系不完善[87]。EVs及其工程化载药系统在临床转化前景广阔，但仍需更多临床前研究和早期临床试验验证其安全性、有效性与可操作性。结合纳米技术、合成生物学和免疫工程等多学科手段，EVs有望在个体化放疗增敏及联合多模态治疗中实现临床应用。

4 总结与展望

EVs作为细胞间信息传递的重要介质，在肿瘤RR的形成与逆转中发挥着双重角色。一方面，肿瘤来源EVs可通过调控DNA损伤修复、细胞周期及凋亡通路等机制，促进RR形成；另一方面，EVs也具备良好的药物递送潜力，能被工程化为高效、安全的放疗增敏载体。当前研究虽揭示其关键作用，但仍受制于异质性、分离纯化及临床转化等瓶颈。未来，EVs有望在以下几个方向实现突破与应用拓展：（1）机制深入研究：通过整合多组学数据，解析不同肿瘤类型中EVs介导RR的关键分子网络；（2）技术平台构建：建立高效、标准化的EVs分离、修饰与功能验证平台，推动其规模化生产与临床应用；（3）治疗策略优化：联合放疗、免疫治疗、靶向治疗等多模态方案，探索EVs作为协同增敏因子的最优使用方式；（4）精准医学融合：结合液体活检技术，利用EVs标志物预测放疗反应、指导个体化治疗决策，实现动态监测与精准干预。

EVs在肿瘤放疗耐药机制研究及增敏治疗策略开发中展现出广阔前景。随着纳米医学、合成生物学与免疫工程等领域的持续发展，EVs有望成为新一代肿瘤放疗个体化治疗的重要平台，为提高疗效与改善预后提供新思路与突破。

作者贡献声明 刘瑄负责查阅文献、收集材料并撰写论文；官成浓负责审阅并修改论文。所有作者均已阅读并同意最终文本

参考文献

1 Filho A M, Laversanne M, Ferlay J, *et al*. The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide [J]. International Journal of Cancer, 2025, **156**(7): 1336-1346. DOI: 10.1002/ijc.35278.

2 Kaur R, Bhardwaj A, Gupta S. Cancer treatment therapies: traditional to modern approaches to combat cancers[J]. Molecular Biology Reports, 2023, **50**(11): 9663-9676. DOI: 10.1007/s11033-023-08809-3.

3 Rakotomalala A, Escande A, Furlan A, *et al*. Hypoxia in solid tumors: how low oxygenation impacts the “six rs” of radiotherapy[J]. Frontiers in Endocrinology, 2021, **12**: 742215. DOI: 10.3389/fendo.2021.742215.

4 Zhou J Y, Lei N J, Tian W J, *et al*. Recent progress of the tumor microenvironmental metabolism in cervical cancer radioresistance[J]. Frontiers in Oncology, 2022, **12**: 999643. DOI: 10.3389/fonc.2022.999643.

5 Jalali-Zefrei F, Mousavi S M, Delpasand K, *et al*. Role of non-coding RNAs on the radiotherapy sensitivity and resistance in cancer cells[J]. Current Gene Therapy, 2025, **25**(2): 113-135. DOI: 10.2174/0115665232301727240422092311.

6 Chen W J, Wu Y L, Deng J J, *et al*. Phospholipid-membrane-based nanovesicles acting as vaccines for tumor immunotherapy: classification, mechanisms and applications[J]. Pharmaceutics, 2022, **14**(11): 2446. DOI: 10.3390/pharmaceutics14112446.

7 Farzam O R, Eslami S, Jafarizadeh A, *et al*. The significance of exosomal non-coding RNAs (ncRNAs) in the metastasis of colorectal cancer and development of therapy resistance[J]. Gene, 2025, **937**: 149141. DOI: 10.1016/j.gene.2024.149141.

8 Zemanek T, Danisovic L, Nicodemou A. Exosomes, their sources, and possible uses in cancer therapy in the era of personalized medicine[J]. Journal of Cancer Research and Clinical Oncology, 2024, **151**(1): 16. DOI: 10.1007/s00432-024-06066-w.

9 Ripoll-Viladomiu I, Prina-Mello A, Movia D, *et al*. Extracellular vesicles and the “six rs” in radiotherapy[J]. Cancer Treatment Reviews, 2024, **129**: 102799. DOI: 10.1016/j.ctrv.2024.102799.

10 Mohammadi A H, Ghazvinian Z, Bagheri F, *et al*. Modification of extracellular vesicle surfaces: an approach for targeted drug delivery[J]. BioDrugs, 2023, **37**(3): 353-374. DOI: 10.1007/s40259-023-00595-5.

11 Wang N, Ma F, Song H, *et al*. Mesenchymal stem cell-derived extracellular vesicles for regenerative applications and radiotherapy[J]. Cell Transplant, 2025, **34**: 9636897241311019. DOI: 10.1177/09636897241311019.

12 Battistelli M, Falcieri E. Apoptotic bodies: particular extracellular vesicles involved in intercellular communication[J]. Biology, 2020, **9**(1): 21. DOI: 10.3390/biology9010021.

13 Fatima A, Sanyal S, Jha G K, *et al*. The enigmatic world of tear extracellular vesicles (EVs) – exploring their role in ocular health and beyond[J]. FEBS Letters, 2025, **599**(10): 1346-1372. DOI: 10.1002/1873-3468.70004.

14 Kumar M A, Baba S K, Sadida H Q, *et al*. Extracellular vesicles as tools and targets in therapy for diseases[J]. Signal Transduction and Targeted Therapy, 2024, **9**(1): 27. DOI: 10.1038/s41392-024-01735-1.

15 李俊俊, 涂文志, 刘勇 . 外泌体检测在肿瘤放化疗中的应用 [J]. 辐射研究与辐射工艺学报 , 2017, **35**(3): 030102. DOI: 10.11889/j.1000-3436.2017.rrj.35.030102.
LI Junjun, TU Wenzhi, LIU Yong. Advances of exosome research in cancer radiotherapy and chemotherapy[J]. Journal of Radiation Research and Radiation Processing, 2017, **35**(3): 030102. DOI: 10.11889/j. 1000-3436.2017.rrj.35.030102.

16 Liu Y J, Wang C. A review of the regulatory mechanisms of extracellular vesicles-mediated intercellular communication[J]. Cell Communication and Signaling, 2023, **21**(1): 77. DOI: 10.1186/s12964-023-01103-6.

17 Zhang N Q, Shu L Z, Liu Z L, *et al*. The role of extracellular vesicles in cholangiocarcinoma tumor microenvironment[J]. Frontiers in Pharmacology, 2024, **14**: 1336685. DOI: 10.3389/fphar.2023.1336685.

18 Dai J, Su Y Z, Zhong S Y, *et al*. Exosomes: key players in cancer and potential therapeutic strategy[J]. Signal Transduction and Targeted Therapy, 2020, **5**(1): 145. DOI: 10.1038/s41392-020-00261-0.

19 Théry C, Witwer K W, Aikawa E, *et al*. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines[J]. Journal of Extracellular Vesicles, 2018, **7**(1): 1535750. DOI: 10.1080/20013078.2018.1535750.

20 Mir R, Baba S K, Elfaki I, *et al*. Unlocking the secrets of extracellular vesicles: orchestrating tumor microenvironment dynamics in metastasis, drug resistance, and immune evasion[J]. Journal of Cancer, 2024, **15**(19): 6383-6415. DOI: 10.7150/jca.98426.

21 Hang Y, Huang J Y, Ding M M, *et al*. Extracellular vesicles reshape the tumor microenvironment to improve cancer immunotherapy: Current knowledge and future prospects[J]. International Immunopharmacology, 2024, **140**: 112820. DOI: 10.1016/j.intimp.2024.112820.

22 Wang L W, Wang D, Ye Z M, *et al*. Engineering extracellular vesicles as delivery systems in therapeutic

applications[J]. Advanced Science, 2023, **10**(17): e2300552. DOI: 10.1002/advs.202300552.

23 Busato F, Khouzai B E, Mognato M. Biological mechanisms to reduce radioresistance and increase the efficacy of radiotherapy: state of the art[J]. International Journal of Molecular Sciences, 2022, **23**(18): 10211. DOI: 10.3390/ijms231810211.

24 Chen T Y, Gonzalez-Kozlova E, Soleymani T, *et al*. Extracellular vesicles carry distinct proteo-transcriptomic signatures that are different from their cancer cell of origin[J]. iScience, 2022, **25**(6): 104414. DOI: 10.1016/j.isci.2022.104414.

25 Shurtleff M J, Yao J, Qin Y D, *et al*. Broad role for YBX1 in defining the small noncoding RNA composition of exosomes[J]. Proceedings of the National Academy of Sciences of the United States of America, 2017, **114**(43): E8987-E8995. DOI: 10.1073/pnas.1712108114.

26 Temoche-Diaz M M, Shurtleff M J, Nottingham R M, *et al*. Distinct mechanisms of microRNA sorting into cancer cell-derived extracellular vesicle subtypes[J]. eLife, 2019, **8**: e47544. DOI: 10.7554/eLife.47544.

27 Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Cabo F, *et al*. Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs[J]. Nature Communications, 2013, **4**: 2980. DOI: 10.1038/ncomms3980.

28 Xing J L, Stea B. Molecular mechanisms of sensitivity and resistance to radiotherapy[J]. Clinical & Experimental Metastasis, 2024, **41**(4): 517-524. DOI: 10.1007/s10585-023-10260-4.

29 Mutschelknaus L, Peters C, Winkler K, *et al*. Exosomes derived from squamous head and neck cancer promote cell survival after ionizing radiation[J]. PLoS One, 2016, **11**(3): e0152213. DOI: 10.1371/journal.pone.0152213.

30 Véquaud E, Desplanques G, Jézéquel P, *et al*. Survivin contributes to DNA repair by homologous recombination in breast cancer cells[J]. Breast Cancer Research and Treatment, 2016, **155**(1): 53-63. DOI: 10.1007/s10549-015-3657-z.

31 Tortolici F, Vumbaca S, Incocciati B, *et al*. Ionizing radiation-induced extracellular vesicle release promotes AKT-associated survival response in SH-SY5Y neuroblastoma cells[J]. Cells, 2021, **10**(1): 107. DOI: 10.3390/cells10010107.

32 Burko P, D'Amico G, Miltykh I, *et al*. Molecular pathways implicated in radioresistance of glioblastoma multiforme: what is the role of extracellular vesicles?[J]. International Journal of Molecular Sciences, 2023, **24**(5): 4883. DOI: 10.3390/ijms24054883.

33 Dutta S, Warshall C, Bandyopadhyay C, *et al*. Interactions between exosomes from breast cancer cells and primary mammary epithelial cells leads to generation of reactive oxygen species which induce DNA damage response, stabilization of p53 and autophagy in epithelial cells[J]. PLoS One, 2014, **9**(5): e97580. DOI: 10.1371/journal.pone.0097580.

34 Sun Y C, Wang J Z, Ma Y, *et al*. Radiation induces NORAD expression to promote ESCC radiotherapy resistance *via* EEPD1/ATR/Chk1 signalling and by inhibiting pri-miR-199a1 processing and the exosomal transfer of miR-199a-5p[J]. Journal of Experimental & Clinical Cancer Research, 2021, **40**(1): 306. DOI: 10.1186/s13046-021-02084-5.

35 Liu Q S, Xin L, Ma X N, *et al*. Dual role of targeting NAE1 in nasopharyngeal carcinoma: Antitumor effects yet inducing radiotherapy resistance[J]. Heliyon, 2024, **10**(17): e37219. DOI: 10.1016/j.heliyon.2024.e37219.

36 Pawlik T M, Keyomarsi K. Role of cell cycle in mediating sensitivity to radiotherapy[J]. International Journal of Radiation Oncology, Biology, Physics, 2004, **59**(4): 928-942. DOI: 10.1016/j.ijrobp.2004.03.005.

37 Vismara M, Zarà M, Negri S, *et al*. Platelet-derived extracellular vesicles regulate cell cycle progression and cell migration in breast cancer cells[J]. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, 2021, **1868**(1): 118886. DOI: 10.1016/j.bbamcr.2020.118886.

38 Jiang M J, Chen Y Y, Dai J J, *et al*. Dying tumor cell-derived exosomal miR-194-5p potentiates survival and repopulation of tumor repopulating cells upon radiotherapy in pancreatic cancer[J]. Molecular Cancer, 2020, **19**(1): 68. DOI: 10.1186/s12943-020-01178-6.

39 Qu P, Shao Z A, Wang B, *et al*. miR-663a inhibits radiation-induced epithelium-to-mesenchymal transition by targeting TGF-β1[J]. Biomedical and Environmental Sciences, 2022, **35**(5): 437-447. DOI: 10.3967/bes2022.059.

40 Zhang J, Li H D, Liu Y, *et al*. Targeting HSP90 as a novel therapy for cancer: mechanistic insights and translational relevance[J]. Cells, 2022, **11**(18): 2778. DOI: 10.3390/cells11182778.

41 Elmore S. Apoptosis: a review of programmed cell death [J]. Toxicologic Pathology, 2007, **35**(4): 495-516. DOI:

10.1080/01926230701320337.

42 Li Y L, Huang L Y, Chen Y C, *et al*. Irradiated cell-derived exosomes transmit essential molecules inducing radiation therapy resistance[J]. International Journal of Radiation Oncology, Biology, Physics, 2022, **113**(1): 192-202. DOI: 10.1016/j.ijrobp.2022.01.036.

43 Khan S, Jutzy J M S, Aspe J R, *et al*. Survivin is released from cancer cells *via* exosomes[J]. Apoptosis, 2011, **16** (1): 1-12. DOI: 10.1007/s10495-010-0534-4.

44 Reichert S, Rödel C, Mirsch J, *et al*. Survivin inhibition and DNA double-strand break repair: a molecular mechanism to overcome radioresistance in glioblastoma [J]. Radiotherapy and Oncology, 2011, **101**(1): 51-58. DOI: 10.1016/j.radonc.2011.06.037.

45 Tang Y T, Cui Y Y, Li Z P, *et al*. Radiation-induced miR-208a increases the proliferation and radioresistance by targeting p21 in human lung cancer cells[J]. Journal of Experimental & Clinical Cancer Research, 2016, **35**: 7. DOI: 10.1186/s13046-016-0285-3.

46 Konishi H, Hayashi M, Taniguchi K, *et al*. The therapeutic potential of exosomal miR-22 for cervical cancer radiotherapy[J]. Cancer Biology & Therapy, 2020, **21**(12): 1128-1135. DOI: 10.1080/15384047.2020. 1838031.

47 Yuan D X, Xu J P, Wang J, *et al*. Extracellular miR-1246 promotes lung cancer cell proliferation and enhances radioresistance by directly targeting DR5[J]. Oncotarget, 2016, **7**(22): 32707-32722. DOI: 10.18632/oncotarget. 9017.

48 Fang J C, Rao X R, Wang C J, *et al*. Role of exosomes in modulating non-small cell lung cancer radiosensitivity[J]. Frontiers in Pharmacology, 2024, **15**: 1471476. DOI: 10.3389/fphar.2024.1471476.

49 Wu Y J, Fu H C, Hao J W, *et al*. Tumor-derived exosomal PD-L1: a new perspective in PD-1/PD-L1 therapy for lung cancer[J]. Frontiers in Immunology, 2024, **15**: 1342728. DOI: 10.3389/fimmu.2024.1342728.

50 Wu B, Huang X, Shi X, *et al*. LAMTOR1 decreased exosomal PD-L1 to enhance immunotherapy efficacy in non-small cell lung cancer[J]. Molecular Cancer, 2024, **23** (1): 184. DOI: 10.1186/s12943-024-02099-4.

51 Zhang Y L, Lyu N, Li M S, *et al*. Cancer-associated fibroblasts: tumor defenders in radiation therapy[J]. Cell Death & Disease, 2023, **14**(8): 541. DOI: 10.1038/ s41419-023-06060-z.

52 Lin Z J, Li G Q, Jiang K, *et al*. Cancer therapy resistance mediated by cancer-associated fibroblast-derived extracellular vesicles: biological mechanisms to clinical significance and implications[J]. Molecular Cancer, 2024, **23**(1): 191. DOI: 10.1186/s12943-024-02106-8.

53 Pasqualetti F, Miniati M, Gonnelli A, *et al*. Cancer stem cells and glioblastoma: time for innovative biomarkers of radio-resistance? [J]. Biology, 2023, **12**(10): 1295. DOI: 10.3390/biology12101295.

54 Silva R O, Haddad M, Counil H, *et al*. Exploring the potential of plasma and adipose mesenchymal stem cell-derived extracellular vesicles as novel platforms for neuroinflammation therapy[J]. Journal of Controlled Release, 2025, **377**: 880-898. DOI: 10.1016/j. jconrel. 2024.11.060.

55 Guo C H, You Y Q, Chen J B, *et al*. Exosomes and non-coding RNAs: bridging the gap in Alzheimer’s pathogenesis and therapeutics[J]. Metabolic Brain Disease, 2025, **40**(1): 84. DOI: 10.1007/s11011-024-01520-7.

56 Chen X J, Liu J Q, Zhang Q L, *et al*. Exosome-mediated transfer of miR-93-5p from cancer-associated fibroblasts confer radioresistance in colorectal cancer cells by downregulating FOXA1 and upregulating TGFB3[J]. Journal of Experimental & Clinical Cancer Research, 2020, **39**(1): 65. DOI: 10.1186/s13046-019-1507-2.

57 Wan F Z, Chen K H, Sun Y C, *et al*. Exosomes overexpressing miR-34c inhibit malignant behavior and reverse the radioresistance of nasopharyngeal carcinoma [J]. Journal of Translational Medicine, 2020, **18**(1): 12. DOI: 10.1186/s12967-019-02203-z.

58 Shan C, Liang Y, Wang K, *et al*. Mesenchymal stem cell-derived extracellular vesicles in cancer therapy resistance: from biology to clinical opportunity[J]. International Journal of Biological Sciences, 2024, **20**(1): 347-366. DOI: 10.7150/ijbs.88500.

59 Zhao X Y, Wu D L, Ma X D, *et al*. Exosomes as drug carriers for cancer therapy and challenges regarding exosome uptake[J]. Biomedicine & Pharmacotherapy, 2020, **128**: 110237. DOI: 10.1016/j.biopha.2020.110237.

60 Zhao S, Di Y F, Fan H L, *et al*. Targeted delivery of extracellular vesicles: the mechanisms, techniques and therapeutic applications[J]. Molecular Biomedicine, 2024, **5**(1): 60. DOI: 10.1186/s43556-024-00230-x.

61 Ai Y W, Guo C X, Garcia-Contreras M, *et al*. Endocytosis blocks the vesicular secretion of exosome marker proteins[J]. Science Advances, 2024, **10**(19):

eadi9156. DOI: 10.1126/sciadv.adi9156.

62 Zhang H, Qin C, An C, *et al*. Application of the CRISPR/Cas9-based gene editing technique in basic research, diagnosis, and therapy of cancer[J]. Molecular Cancer, 2021, **20**(1): 126. DOI: 10.1186/s12943-021-01431-6.

63 Zhang Z F, Liu X, Chen D W, *et al*. Radiotherapy combined with immunotherapy: the dawn of cancer treatment[J]. Signal Transduction and Targeted Therapy, 2022, **7**(1): 258. DOI: 10.1038/s41392-022-01102-y.

64 Guo S Y, Yao Y H, Tang Y, *et al*. Radiation-induced tumor immune microenvironments and potential targets for combination therapy[J]. Signal Transduction and Targeted Therapy, 2023, **8**(1): 205. DOI: 10.1038/s41392-023-01462-z.

65 Manoochehri H, La'ah A S, Babaeizad A, *et al*. Extracellular vesicles in cancer immunotherapy: therapeutic, challenges and clinical progress[J]. Asian Journal of Pharmaceutical Sciences, 2025: 101065. DOI: 10.1016/j.ajps.2025.101065.

66 Storozynsky Q, Hitt M M. The impact of radiation-induced DNA damage on cGAS-STING-mediated immune responses to cancer[J]. International Journal of Molecular Sciences, 2020, **21**(22): 8877. DOI: 10.3390/ijms21228877.

67 Wang Q Y, Yu Y, Zhuang J, *et al*. Demystifying the cGAS-STING pathway: precision regulation in the tumor immune microenvironment[J]. Molecular Cancer, 2025, **24**(1): 178. DOI: 10.1186/s12943-025-02380-0.

68 Liang J Q, Yin H. STAM transports STING oligomers into extracellular vesicles, down-regulating the innate immune response[J]. Journal of Extracellular Vesicles, 2023, **12**(3): e12316. DOI: 10.1002/jev2.12316.

69 吴迅, 刘锐锋, 张秋宁, 等. FLASH放射生物学机制及治疗计划研究进展[J]. 辐射研究与辐射工艺学报, 2023, **41**(2): 020101. DOI: 10.11889/j. 1000-3436.2022-0074.

WU Xun, LIU Ruifeng, ZHANG Qiuning, *et al*. Radiobiology and treatment plan progress of FLASH radiotherapy[J]. Journal of Radiation Research and Radiation Processing, 2023, **41**(2): 020101. DOI: 10.11889/j.1000-3436.2022-0074.

70 Lin F, Yin H B, Li X Y, *et al*. Bladder cancer cell-secreted exosomal miR-21 activates the PI3K/AKT pathway in macrophages to promote cancer progression[J]. International Journal of Oncology, 2020, **56**(1): 151-164. DOI: 10.3892/ijo.2019.4933.

71 Qian M Y, Wang S B, Guo X F, *et al*. Hypoxic glioma-derived exosomes deliver microRNA-1246 to induce M2 macrophage polarization by targeting $TERF_2IP$ *via* the STAT3 and NF-κB pathways[J]. Oncogene, 2020, **39**(2): 428-442. DOI: 10.1038/s41388-019-0996-y.

72 Zhang X, Shi H, Yuan X, *et al*. Tumor-derived exosomes induce N_2 polarization of neutrophils to promote gastric cancer cell migration[J]. Molecular Cancer, 2018, **17**(1): 146. DOI: 10.1186/s12943-018-0898-6.

73 Shinde-Jadhav S, Mansure J J, Rayes R F, *et al*. Role of neutrophil extracellular traps in radiation resistance of invasive bladder cancer[J]. Nature Communications, 2021, **12**(1): 2776. DOI: 10.1038/s41467-021-23086-z.

74 Zhang F Y, Mulvaney O, Salcedo E, *et al*. Radiation-induced innate neutrophil response in tumor is mediated by the CXCLs/CXCR2 axis[J]. Cancers, 2023, **15**(23): 5686. DOI: 10.3390/cancers15235686.

75 Hosseini R, Sarvnaz H, Arabpour M, *et al*. Cancer exosomes and natural killer cells dysfunction: biological roles, clinical significance and implications for immunotherapy[J]. Molecular Cancer, 2022, **21**(1): 15. DOI: 10.1186/s12943-021-01492-7.

76 Zhang Y, Hu R M, Xi B X, *et al*. Mechanisms of senescence-related NKG2D ligands release and immune escape induced by chemotherapy in neuroblastoma cells [J]. Frontiers in Cell and Developmental Biology, 2022, **10**: 829404. DOI: 10.3389/fcell.2022.829404.

77 Li H Z, Chen X, Zheng S S, *et al*. The expansion of MDSCs induced by exosomal PD-L1 promotes the progression of gastric cancer[J]. Journal of Translational Medicine, 2024, **22**(1): 821. DOI: 10.1186/s12967-024-05611-y.

78 Yu S L, Jiang S S, Zhou Y, *et al*. Impact of radiation on exosomes in regulating tumor immune microenvironment [J]. Advances in Radiation Oncology, 2024, **9**(8): 101549. DOI: 10.1016/j.adro.2024.101549.

79 Zhang J, Wu J M. The potential roles of exosomal miR-214 in bone metastasis of lung adenocarcinoma[J]. Frontiers in Oncology, 2021, **10**: 611054. DOI: 10.3389/fonc.2020.611054.

80 Lyu C, Sun H F, Sun Z Q, *et al*. Roles of exosomes in immunotherapy for solid cancers[J]. Cell Death & Disease, 2024, **15**(2): 106. DOI: 10.1038/s41419-024-06494-z.

81 Hu Q, Chen S, Deng R L, *et al*. Exosomal PDL1 suppresses the anticancer activity of $CD8^+$ T cells in

hepatocellular carcinoma[J]. Analytical Cellular Pathology, 2024, **2024**: 1608582. DOI: 10.1155/2024/1608582.

82 Ahn M, Mun J G, Han Y, *et al*. Cancer cell-derived extracellular vesicles: a potential target for overcoming tumor immunotherapy resistance and immune evasion strategies[J]. Frontiers in Immunology, 2025, **16**: 1601266. DOI: 10.3389/fimmu.2025.1601266.

83 Mortezaee K, Majidpoor J. Extracellular vesicle-based checkpoint regulation and immune state in cancer[J]. Medical Oncology, 2022, **39**(12): 225. DOI: 10.1007/s12032-022-01837-2.

84 Zhou G, Gu Y, Zhu Z, *et al*. Exosome mediated cytosolic cisplatin delivery through clathrin-independent endocytosis and enhanced anti-cancer effect via avoiding endosome trapping in cisplatin-resistant ovarian cancer [J]. Front Med (Lausanne), 2022, **9**: 810761.

85 Lv Q J, Cheng L L, Lu Y, et al. Thermosensitive exosome-liposome hybrid nanoparticle-mediated chemoimmunotherapy for improved treatment of metastatic peritoneal cancer[J]. Advanced Science, 2020, 7(18): 2000515. DOI: 10.1002/advs.202000515.

86 Shami-Shah A, Travis B G, Walt D R. Advances in extracellular vesicle isolation methods: a path towards cell-type specific EV isolation[J]. Extracellular Vesicles and Circulating Nucleic Acids, 2023, **4**(3): 447-460. DOI: 10.20517/evcna.2023.14.

87 Huang C, Li H, Zhang Z Y, *et al*. From mechanism to therapy: the role of MSC-EVs in alleviating radiation-induced injuries[J]. Pharmaceutics, 2025, **17**(5): 652. DOI: 10.3390/pharmaceutics17050652.

88 Liu M W, Li H, Xiong G F, *et al*. Mesenchymal stem cell exosomes therapy for the treatment of traumatic brain injury: mechanism, progress, challenges and prospects[J]. Journal of Translational Medicine, 2025, **23**(1): 427. DOI: 10.1186/s12967-025-06445-y.