Exosomal circular RNAs in the tumor immune microenvironment: From regulatory mechanisms to therapeutic opportunities and translational hurdles (Review)

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Abstract. Immune checkpoint inhibitors have changed cancer treatment, although durable benefit remains limited because malignant, immune and stromal cells sustain suppression within the tumor immune microenvironment. Extracellular vesicles (EVs), including small EVs, can transfer circular RNAs (circRNAs) between defined donor and recipient cells. The relevant steps extend from circRNA biogenesis and entry into EV populations to delivery, intracellular activity, immune phenotype and clinical use. Incomplete transfer experiments, tumor-intrinsic circRNA activity and engineered RNA platforms differ from direct EV-mediated transfer. Direct transfer has been linked to tumor-associated macrophages, myeloid-derived suppressor cells, natural killer cells, $CD8^+$ T cells and regulatory T cells. Within recipient cells, circRNAs can regulate microRNA availability, assemble RNA-binding protein complexes, alter protein or RNA stability and produce functional peptides. Donor state, recipient identity, tissue site, EV subpopulation and delivered dose can change the resulting phenotype. Cancer-associated fibroblasts further connect EV-associated circRNAs with matrix remodeling, immune-cell access and treatment tolerance. Biological support is classified from E0 to E3, while EV methods are considered separately through source definition, separation, characterization, RNA protection, uptake controls and quantitative dose. Translation will require full-length circRNA identification, absolute measurement in EVs and recipient cells, spatial localization, prospective treatment cohorts and repeated-dose safety testing. These requirements distinguish circulating associations from transferred molecules and identify the experiments needed for biomarker or therapeutic development.

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Contents

1. Introduction

Immune checkpoint inhibitors (ICIs) directed against programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can produce durable responses in several cancers, although numerous patients do not respond (1,2). T-cell dysfunction and exclusion describe distinct immune states associated with treatment response, while the distribution of PD-1, programmed death ligand 1 (PD-L1) and immune cells within tumors further separates responsive from resistant lesions (3,4). These states arise within a multicellular system in which cytotoxic lymphocytes

encounter suppressive signals from myeloid and stromal cells. Extracellular vesicle (EV)-mediated communication provides one route by which these signals move between cellular compartments. Early experiments showed that EV preparations transfer functional mRNA and microRNA (miRNA or miR) between cells (5). Tumor EVs can also suppress T cells through CD39 and CD73, and tumor-macrophage communication can amplify adenosine production during PD-1 blockade (6,7). Serum EV-associated CD73 has likewise been linked to lymphocyte suppression and anti-PD-1 outcomes in melanoma (8).

Circular RNAs (circRNAs) arise through back-splicing and form covalently closed molecules that often resist exonuclease degradation (9,10). N^6-methyladenosine (m^6A) can alter their recognition by innate immune sensors, which links RNA modification to the immune response elicited by endogenous and engineered circRNAs (11). CircRNAs are enriched and stable in some EV preparations, two properties relevant to intercellular signaling and circulating biomarker development (12). A complete transfer process begins with circRNA production in a donor cell. It then requires entry into a defined EV population, protection outside the cell, uptake by a specified recipient and delivery of enough intact RNA to the intracellular site where the proposed molecular event occurs. Detection in an EV preparation establishes association with that preparation. Selective entry, recipient specificity and intracellular activity require separate measurements. Within this sequence, transfer into defined immune recipient cells has been measured in several tumor systems. In hepatocellular carcinoma (HCC), EV-associated circUHRF1 entered natural killer (NK) cells and was linked to reduced effector function and lower anti-PD-1 activity, while EV-associated circCCAR1 entered $CD8^+$ T cells and prolonged PD-1 protein stability (13,14). In non-small cell lung cancer (NSCLC), EV-associated circUSP7 reduced $CD8^+$ T-cell function, and bladder cancer-derived EV-associated circTRPS1 was linked to T-cell exhaustion and tumor-cell glutamine metabolism (15,16). In lung adenocarcinoma (LUAD), EV-associated circZNF451 acted in macrophages through a TRIM56-FXR1 complex and reduced the response to PD-1 blockade in mice (17). These mechanisms occur in different recipient cells and do not share a single intracellular route (Table SI).

Tumor-intrinsic circRNAs address a related biological question because they can change checkpoint abundance or chemokine signaling without being transferred. In colorectal cancer (CRC), hsa_circ_0020397 increased TERT and PD-L1 (18). CircMET was linked to immunosuppression and anti-PD-1 resistance in HCC, whereas circ_0020710 increased CXCL12-dependent immune escape in melanoma (19,20). Stromal context adds another route. Pancreatic cancer-associated fibroblasts (CAFs) include inflammatory and myofibroblastic populations, and single-cell analysis has also identified antigen-presenting CAF states (21,22). EV-associated circEHD2 activated fibroblasts in renal cell carcinoma (RCC), while CAF-derived EV-associated circEIF3K altered CRC-cell PD-L1 and endothelial behavior (23,24). A circRNA-induced stromal state may therefore lie one step upstream of immune-cell access when that stromal state is independently known to restrict infiltration (25). Direct immune regulation requires the circRNA, stromal change and immune-cell distribution to be measured in the same model.

Four levels describe the biological support for each reported process. E0 denotes biological background and adjacent engineered platforms. E1 denotes an association or a transfer process with one or more untested steps. E2 requires a defined donor, an EV population, a recipient and a mechanistic cellular endpoint. E3 adds circRNA-specific perturbation, rescue, an immune function, *in vivo* validation and a treatment endpoint. EV methods are evaluated independently because source handling, separation and co-isolated material affect interpretation at every biological level. Minimal Information for studies of extracellular vesicles 2023 (MISEV2023) guides terminology and experimental reporting (26). The terms EV or small EV (sEV), rather than exosome, are therefore used when endosomal origin has not been established.

2. Loading, delivery and intra-recipient modes of action of exosomal circRNAs

The activity of an EV-associated circRNA depends on sequential events that can vary independently. Donor-cell expression can rise without preferential entry into EVs, and an increased signal in an EV preparation can reflect greater particle release or RNA outside vesicles. In glioma, EWSR1 increased circNEIL3 in donor cells and EVs, while hnRNPA2B1 supported EV association and transfer to macrophages (27). hnRNPA2B1 can recognize RNA motifs during miRNA sorting, and small molecules that interrupt hnRNPA2B1-RNA interactions alter defined subsets of EV RNA (28,29). For an individual circRNA, selective entry therefore requires direct RNA-binding protein (RBP) binding, donor-cell perturbation, normalization to particle number and exclusion of changes in cell viability or total EV release. Selective entry also requires the identity of the transferred RNA to be established beyond its back-splice junction. Long-read sequencing has shown that one junction can represent several full-length circRNA isoforms with different internal exons, RBP-binding regions and open reading frames (30). In *Schizosaccharomyces pombe*, circRNA biogenesis proceeded through an exon-containing lariat precursor, providing an alternative route to circularization (31). Divergent primers, junction sequencing and RNase R treatment establish circularity, while long-read or targeted full-length sequencing identifies the transferred isoform. These steps become necessary when the proposed mechanism depends on an internal binding site or a translated sequence (Fig. 1).

Delivery depends on EV properties and conditions in the recipient tissue. Tumor EV integrins can influence organ distribution, while paracrine adhesion signaling can increase sEV uptake by selected cells (32,33). Neither process shows that a named circRNA determines recipient specificity. Fluorescent membrane signals can also persist in endosomes or arise from dye particles. Functional delivery therefore requires RNA protection before uptake, an increase in intact circRNA within the recipient, access to the relevant intracellular compartment and loss of activity when uptake or intracellular release is blocked. MISEV2023 places these controls alongside source definition, separation, particle characterization and analysis of non-vesicular material (26). Even after uptake is established,

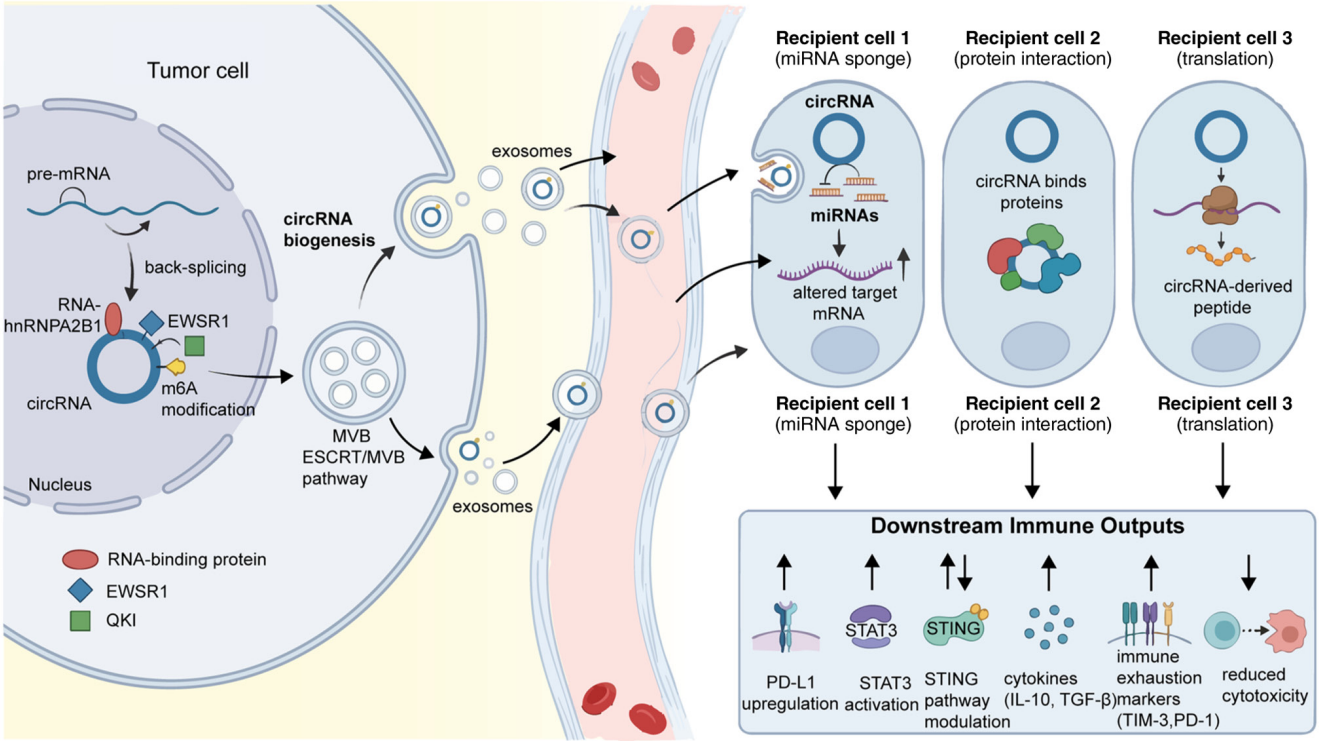

Figure 1. Exosomal circRNA generation, selective loading and functional modes in the tumor immune microenvironment. Schematic overview of the life cycle and major functional modes of exosomal circRNAs in cancer. CircRNAs generated by back-splicing in donor cells may be selectively loaded into intraluminal vesicles during multivesicular body formation, a process influenced by RNA-binding proteins and RNA modifications. Released exosomes can be taken up by immune cells and stromal cells. In recipient cells, circRNAs act through three principal modes including miRNA sequestration, protein binding and scaffolding, and translation into functional peptides. These modes converge on immune-relevant outcomes such as macrophage polarization, NK-cell dysfunction, $CD8^+$ T-cell exhaustion, altered cytokine programs and modulation of immune checkpoint pathways. circRNA, circular RNA; miRNAs, microRNAs; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1.

bulk EV measurements obscure particle-to-particle variation and the dose received by individual cells. Single-EV transcriptomic analysis detected transcripts from 6 to 148 genes per EV, with a mean of 52, but did not measure copies of a specific circRNA in each vesicle (34). SVAtlas integrates single-EV protein, RNA, DNA, lipid and metabolite datasets and permits comparison of EV subpopulations across tissues and diseases (35). These resources establish heterogeneity without supplying a universal circRNA copy number. Dose analysis should instead report particles per recipient cell, the fraction of particles containing the circRNA, copies per positive particle, cytosolic delivery efficiency and target abundance.

miRNA regulation depends on the same quantitative constraints. Experiments in hepatocytes found threshold-like release of miRNA repression only after a large increase in target-site abundance (36). Measurements of endogenous miRNA and target pools further showed that competition varies with their relative abundance and binding affinity (37). Binding, reporter activity and target rescue do not by themselves establish competition at physiological concentrations (38). An EV-associated competing endogenous RNA model should include the amount of circRNA delivered, Argonaute 2 occupancy, miRNA abundance and the available cellular target pool. These quantitative constraints apply directly to transferred circRNAs linked to miRNA-dependent changes, although molecular ratios remain unresolved. In gastric cancer (GC), sEV-associated circ_0001947 entered $CD8^+$ T cells and regulated miR-661, miR-671-5p and CD39 during anti-PD-1 treatment (39). EV-associated circPACRGL acted through miR-142-3p, miR-506-3p and transforming growth factor-β1 in CRC cells (40). Transfer was linked to specific miRNAs and downstream proteins. Competition at the delivered dose still depends on absolute abundance and target-site occupancy.

Mechanisms that do not depend on miRNA competition require a different set of tests. In pancreatic ductal adenocarcinoma (PDAC), m^6A-modified circMYO1C was linked to PD-L1 regulation, while circ_0074158 interacted with QKI6 and altered PD-L1 ubiquitination in NSCLC (41,42). A peptide encoded by circHNRNPU changed alternative splicing and the bone-marrow environment in multiple myeloma (43). Tumor circRNAs can also generate cryptic peptides that enter antigen-presentation pathways and elicit antitumor T-cell responses (44). Each route requires a different perturbation. Protein-complex models require mapped binding sites and rescue. Translation requires full-length sequence definition, disruption of the open reading frame, peptide detection and restoration by the peptide product. The same separation between route and endpoint applies when EV-associated circRNAs act through tumor or vascular cells rather than immune cells. Exosomal hsa_circ_0051443 transferred from normal liver cells to HCC cells and suppressed tumor-cell growth, whereas HCC-derived EV-associated circRNA-100338 increased invasion and angiogenesis (45,46). Microglia-derived EV-associated circKIF18A increased glioblastoma angiogenesis through FOXC2 (47). EV-associated circRNAs can therefore change vascular or tumor features

in the immune-cell environment. Immune cells were not the recipients in these models. Testing their immune relevance requires measurement of the affected vascular or tumor state together with immune-cell position and function.

3. Exosomal circRNA-mediated reprogramming of tumor-associated macrophages (TAMs) and its links to metastasis and immunotherapy outcomes

TAM states vary with tissue of origin, tumor stage, local signals and treatment. M1 and M2 describe two ends of a broader functional range and cannot be assigned from one marker. EV-associated circRNAs can alter macrophage signaling, metabolism and cytokine production, after which macrophages can change tumor invasion, distant colonization or lymphocyte function. A transfer experiment therefore needs a donor cell, an EV preparation, recipient macrophages, an intracellular circRNA change and a macrophage-dependent endpoint. Within this functional range, tumor-derived EV-associated circRNAs often shift macrophages toward states linked to invasion or metastasis. In NSCLC, circFARSA acted through PTEN-PI3K-AKT signaling, while circATP9A combined HuR binding in tumor cells with EV-mediated macrophage regulation (48,49). Hypoxia increased EV-associated circ0048117 in esophageal squamous cell carcinoma (ESCC), linking donor oxygen status to macrophage exposure (50). In epithelial ovarian cancer, EV-associated circATP2B4 regulated miR-532-3p, SREBF1 and PI3K-AKT signaling in macrophages (51). In HCC, reduced hsa_circ_0074854 altered HuR-associated tumor behavior and macrophage polarization through EVs (52). The donor state and molecular route therefore differ even when the recipient phenotype shares CD163 or CD206 expression.

Some circRNAs change the molecular contents of EVs without being transferred themselves. In CRC cells, circASPH stabilized IGF2BP2 and increased m^{6}A-modified STING RNA, which raised EV-associated STING and altered macrophages (53). In the aforementioned study, STING was transferred and circASPH remained tumor intrinsic. Direct circRNA transfer was shown for several other models. CircPOLQ activated IL-10-STAT3 signaling in CRC macrophages, and circUBQLN1 regulated the miR-34c-5p-CSF1R pathway (54,55). Breast cancer (BC) EV-associated circ-0100519 acted through USP7 and NRF2, while glioma EV-associated circ-001422 increased macrophage polarization associated with tumor growth (56,57). GC EV-associated hsa_circ_0017252 produced the opposite direction and reduced macrophage CD163 and CD206 features together with tumor growth (58).

Communication also proceeds in the opposite direction, with macrophages providing EV-associated circRNAs to tumor cells. M2 macrophage-derived sEV-associated circFTO increased NSCLC malignancy through miR-148a-3p and PDK4, while macrophage EV-associated circRNA_CCDC66 increased CRC immune escape through miR-342-3p and metadherin (59,60). In cholangiocarcinoma (CCA), TAM-derived EV-associated circ_0020256 promoted tumor progression (61). TAM-derived hsa_circ_0001610 reduced endometrial cancer radiosensitivity, which places its endpoint in treatment tolerance rather than ICI response (62). In HCC, M1 macrophage-derived EV-associated miR-628-5p reduced m^{6}A modification of tumor-cell circFUT8 and suppressed progression (63). The transferred molecule in this last model was a miRNA, while the circRNA changed within the recipient tumor cell. Macrophage states can also change without circRNA transfer through tumor-intrinsic circRNAs that regulate recruitment or activation. hsa_circ_0110102 reduced macrophage activation through PPARα and CCL2 in HCC, whereas circHSPB6 increased CCL2-associated macrophage infiltration in LUAD (64,65). CircSMARCC1 regulated a miR-1322-CCL20-CCR6 interaction between prostate cancer cells and TAMs (66). KRAS-associated circHIPK3-PTK2 signaling was linked to macrophage infiltration in lung tumors, while circITGB6 shifted macrophage polarization during cisplatin resistance in ovarian cancer (67,68). Smoking-induced macrophage EV-associated circEML4 acted in NSCLC cells through ALKBH5-dependent m^{6}A regulation of SOCS2 (69). These processes differ in where the circRNA acts and should remain separate from donor-to-macrophage circRNA transfer.

Interventions in the tumor-macrophage interaction have been assessed against tumor growth, metastasis or checkpoint response. Nanoparticle delivery of si-cSERPINE2 reduced breast tumor growth and macrophage-associated suppression (70). In CRC, depletion of EV-associated circ-0034880 reduced SPP1$^+$CD206$^+$ macrophages and liver premetastatic niche formation (71). In HCC, EV-associated hsa_circ_0057320 regulated miR-28-5p and E2F6 during macrophage metabolic reprogramming, angiogenesis and metastasis (72). In glioblastoma, spatial and single-cell analyses identified circSDHAF2, ITGA5 and SPP1$^+$ monocyte-derived macrophages in anti-PD-1 resistance, while ITGA5 blockade restored treatment activity in mice (73). Growth, angiogenesis and metastasis were the HCC endpoints. By contrast, the glioblastoma model included checkpoint treatment and measured macrophage remodeling together with ICI response. Among these routes, EV-associated circZNF451 directly connects macrophage reprogramming with impaired T-cell function. LUAD-derived circZNF451 entered macrophages, assembled with TRIM56 and FXR1, promoted FXR1 degradation and increased ELF4-IRF4 signaling. The resulting macrophages impaired CD8$^+$ T-cell proliferation and effector function, and macrophage-specific ELF4 deletion restored anti-PD-1 activity in mice (17). Metastatic growth, macrophage markers, T-cell suppression and ICI response remain distinct endpoints unless each is measured in the same model.

4. Cross-module regulation by exosomal circRNAs across the myeloid lineage

Myeloid-derived suppressor cells (MDSCs), neutrophils and dendritic cells (DCs) arise within the myeloid compartment, although circRNAs act through different routes in these cells. A tumor-derived EV-associated circRNA can enter a myeloid cell. Myeloid EVs can also transfer another molecule that changes a circRNA in tumor cells. Tumor-intrinsic circRNAs can alter myeloid recruitment without EV transfer. These routes should be identified before their effects on T cells are connected. MDSC-associated models include both transferred circRNAs and tumor-cell circRNAs induced by another transferred molecule. In castration-resistant prostate

cancer, MDSC-derived EVs transferred S100A9 to tumor cells. S100A9 reduced DHX9, increased tumor-cell circMID1 and activated a circMID1-miR-506-3p-MID1 pathway (74). The transferred molecule was S100A9. In bladder cancer, tumor-derived EV-associated circRNA_0013936 entered polymorphonuclear MDSCs, increased fatty acid transport protein 2, reduced receptor-interacting protein kinase 3 and suppressed $CD8^+$ T-cell activity (75). BC Circ-E-cadherin encoded C-E-cad, which increased MDSC recruitment and function without an EV-circRNA transfer experiment (76). In CRC, tumor-intrinsic circNCOA3 was linked to MDSC accumulation and anti-PD-1 resistance (77).

Neutrophil-associated findings remain closer to circulating association or tissue state than to direct transfer. Plasma EV-associated circ-PTPN22 and circ-ADAMTS6 were identified in an intrahepatic CCA (iCCA) cohort with transcriptomic features linked to T-cell exhaustion and neutrophil extracellular traps (78). Only six patients provided plasma EV samples, and no donor-to-neutrophil transfer was tested. CircRERE-PMN was identified in premetastatic lungs and linked to neutrophil-associated changes before metastatic growth (79). Neutrophil membrane-coated nanoparticles carrying circRNA provide a therapeutic delivery system for HER2-positive BC brain metastasis, but they do not model natural EV transfer (80).

In DCs, circRNAs act through endogenous regulation, tumor-cell programs or engineered delivery. CircSnx5 acted within DCs through miR-544, SOCS1 and PU.1 and changed their immunogenic activity (81). Tumor-intrinsic cEMSY induced immunogenic cell death and increased immunotherapy activity in LUAD (82). HCC-derived EV-associated circTMEM56 was linked to miR-136-5p, STING and radiotherapy response (83). Nanochannel electro-injection can introduce RNA or DNA into DCs, although this platform does not reproduce EV loading, release or uptake (84).

The myeloid routes therefore begin at experimentally separate points. CircRNA_0013936 follows tumor cell to EV to MDSC and then reaches a T-cell endpoint. CircMID1 rises in tumor cells after MDSC EV transfer of S100A9. Circ-PTPN22 and circ-ADAMTS6 remain circulating associations. CircSnx5 and cEMSY act inside the cells in which they were manipulated. This separation preserves the direction of communication and prevents an association with a myeloid state from being presented as transferred circRNA activity.

5. Exosomal and tumor-intrinsic circRNAs jointly regulate NK-cell effector function and exhaustion

NK-cell activity depends on activating ligands on tumor cells, inhibitory receptors on NK cells and the metabolic state of both cells during contact. EV-associated circRNAs can act inside NK cells, while tumor-intrinsic circRNAs can change the surface recognized by NK cells. These routes meet at the tumor-NK interface but begin in different cells. In HCC, EV-associated circUHRF1 entered NK cells, reduced miR-449c-5p, increased TIM-3 and lowered IFN-γ and TNF-α secretion. CircUHRF1 was also higher in a small retrospective cohort with progressive disease during anti-PD-1 treatment, and donor-cell depletion restored NK-cell activity in preclinical models (13). The patient cohort does not constitute prospective biomarker validation, and the EV dose did not include the absolute number of circUHRF1 molecules delivered to each NK cell.

A second transferred circRNA reaches NK cells through metabolic injury rather than inhibitory-receptor signaling. CircPDSS1 regulated miR-142-3p and ACSL4, increased lipid peroxidation and ferrous iron and promoted ferroptosis in NK-92 cells. Donor-cell depletion reduced NK-cell death and restored cytokine secretion in coculture and humanized mouse models (85). This process differs from checkpoint-dependent exhaustion because it reduces viable NK cells through iron-dependent lipid damage.

By comparison, tumor-intrinsic circRNAs alter the tumor-cell side of NK-cell contact. In HCC cells, androgen receptor-suppressed CircARSP91 increased UL16-binding protein 1 and enhanced NK-cell cytotoxicity (86). hsa_circ_0007456 increased intercellular adhesion molecule 1 through miR-6852-3p and strengthened NK-cell elimination of HCC cells (87). In bladder cancer, androgen receptor and ADAR2 regulated circ_0001005 and PD-L1, thereby changing NK-cell activity (88). CircARAP2 regulated soluble MICA-associated NK-cell desensitization through RAB5A and endosomal signaling (89). These tumor-cell mechanisms influence ligand availability or inhibitory signaling without EV transfer to NK cells.

Beyond surface ligands, tumor-cell metabolic and interferon programs also change susceptibility to NK-cell attack. CircSpdyA encoded a 127-amino-acid peptide that increased fatty-acid synthesis and reduced NK-cell activity in BC (90). CircFOXO3 was associated with clear-cell RCC proliferation and NK-cell cytotoxicity through miR-29a-3p and miR-122-5p (91). CircRNF10 regulated PTEN-PI3K-AKT signaling and NK-cell-mediated elimination in BC cells (92). In sarcoma, circCsnk1g3 and circAnkib1 altered interferon responses and the immune environment (93). These tumor-cell states can increase or reduce NK-cell function. Direct transfer into NK cells was shown for circUHRF1 and circPDSS1, while the other circRNAs were manipulated within tumor cells (Fig. 2).

6. Bidirectional communication through CAF-associated exosomal circRNAs drives stromal remodeling, restricts immune infiltration and promotes therapy tolerance

CAFs can receive tumor-derived EVs and release EVs to tumor, endothelial and immune cells. Their response depends on tissue site and cellular state. In pancreatic cancer, inflammatory, myofibroblastic and antigen-presenting CAF populations occupy different transcriptional states (21,22). Across other tumors, CAF-derived signals induced PD-L1-positive neutrophils or increased PD-L1 in tumor cells (94,95). CAFs increased PD-L1 in CRC cells through AKT phosphorylation, while PD-L1-positive CAFs were associated with immune suppression in esophageal cancer (96,97). Fibroblast state can therefore precede immune-cell access or checkpoint exposure, although these processes do not identify an EV-associated circRNA by themselves. One direction of EV communication runs from tumor cells to fibroblasts. In RCC, hnRNPA2B1 supported circEHD2 entry into tumor EVs, and fibroblast uptake increased α-smooth muscle actin, fibroblast activation protein

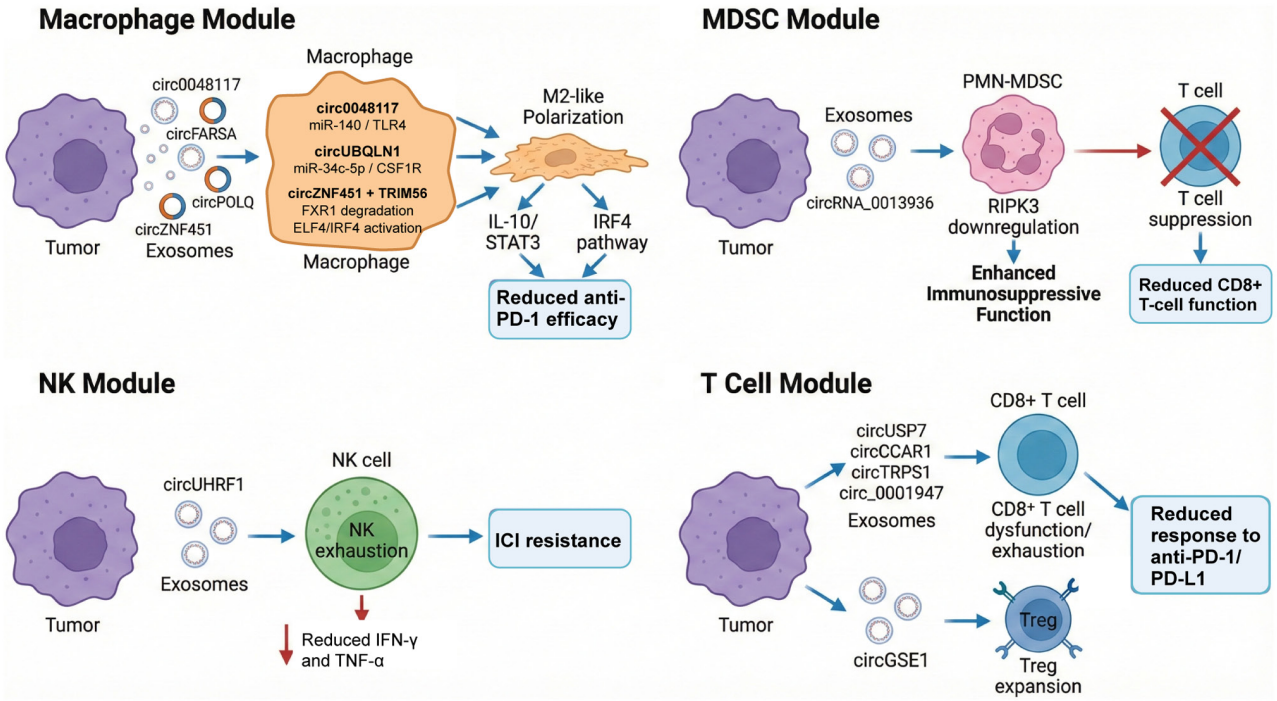

Figure 2. Parallel immune lineage modules targeted by exosomal circRNAs converge on immune suppression and reduced response to immune checkpoint blockade. Representative mechanisms by which tumor-derived or microenvironment-derived exosomal circRNAs reprogram immune lineages. Tumor exosomal circRNAs promote immunosuppressive macrophage polarization and reinforce cytokine programs linked to immune evasion. Tumor exosomal circRNAs can also enhance the suppressive activity of myeloid-derived suppressor cells and impair NK-cell cytotoxicity. In adaptive immunity, exosomal circRNAs contribute to $CD8^+$ T-cell dysfunction and exhaustion and can support regulatory T cell expansion. These lineage-specific effects converge on diminished antitumor immunity and reduced sensitivity to PD-1 or PD-L1 blockade. Representative examples included in the schematic are circUHRF1 in NK-cell dysfunction, circUSP7 and circCCAR1 in $CD8^+$ T-cell dysfunction, and circZNF451 in macrophage polarization. circRNA, circular RNA; NK, natural killer; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; ICI, immune checkpoint inhibitor; MDSC, myeloid-derived suppressor cell.

and tumor-supporting activity (23). Benzo[a]pyrene exposure induced an HCC EV-associated circRNA program that activated lung fibroblasts before organotropic metastasis (98). Hypoxic ESCC cells released EV-associated circNRIP1, which activated fibroblasts and increased tumor-cell migration and invasion (99). EV communication moves in both directions between malignant and stromal cells. Each circRNA nevertheless requires donor- and recipient-specific controls (Fig. 3 and Table SII).

Stromal conversion can expand the population that releases fibroblast-derived EVs, establishing the reverse direction of communication. In GC, sEV-associated circ6718 regulated miR-561-3p, SAAL1, PRRX1 and TGF-β1 and promoted conversion of tumor-derived mesenchymal stem cells into CAFs (100). In high-grade serous ovarian cancer, CAF EV-associated circMPP6 was loaded through hnRNPA2B1 and regulated ADAM22 in tumor cells through nuclear SFPQ-NONO binding and cytoplasmic EEF1A2 binding (101). ADAM22 then activated TGF-β-Smad signaling and metastatic behavior. Both routes end in a defined tumor-cell program without measurements of immune-cell infiltration. Numerous CAF-to-tumor routes then use miRNA-dependent regulation. CircN4BP2L2 increased CRC proliferation and metastasis through miR-664b-3p and HMGB3, while CAF EVs increased tumor-cell circ_0067557 and Lin28 during CRC growth and chemoresistance (102,103). Circ_0084043 increased endothelial tube formation *in vitro* through miR-140-3p, HIF-1α and VEGF (104). The endpoint was an *in vitro* vascular assay. Therefore, immune-cell access and *in vivo* angiogenesis were not measured. In hypoxic BC, CAF EV-associated circHIF1A increased tumor-cell stemness through miR-580-5p and CD44 (105). Hypoxic CAF EV-associated circSTAT3 and circFOXO1 increased triple-negative BC (TNBC) stemness or radioresistance through NOTCH1 and BNIP3, respectively (106,107). The same direction of communication occurs in ESCC, BC and pituitary adenoma. Circ_0076535 increased ESCC progression, and circTBPL1 supported BC growth through intercellular transfer (108,109). Pituitary tumor-associated fibroblast EV-associated circDennd1b regulated miR-145-5p, ONECUT2 and MAPK signaling (110). The measured endpoints were tumor-cell proliferation, invasion or treatment response. They should not be extended to T-cell exclusion without measurements of lymphocyte position or function.

Other CAF-derived circRNAs act through protein binding, translation or stromal feedback rather than miRNA competition. In PDAC, CAF EV-associated circBIRC6 bound XRCC4, increased XRCC4 SUMOylation at K115 and supported non-homologous end joining during oxaliplatin treatment (111). Mutation of XRCC4 K115 and circBIRC6 depletion reduced repair, and combined circBIRC6 inhibition with olaparib suppressed resistant models. In TNBC, CAF EV-associated circMIB1 entered tumor cells and produced MIB1-223aa after uptake. The peptide stabilized MIB1, activated DLL4-Notch signaling and increased metastasis and stemness (112). The peptide was not detected in EVs, which locates translation inside the recipient tumor cell. CRC provides a reciprocal CAF-tumor process. ITGA11-positive

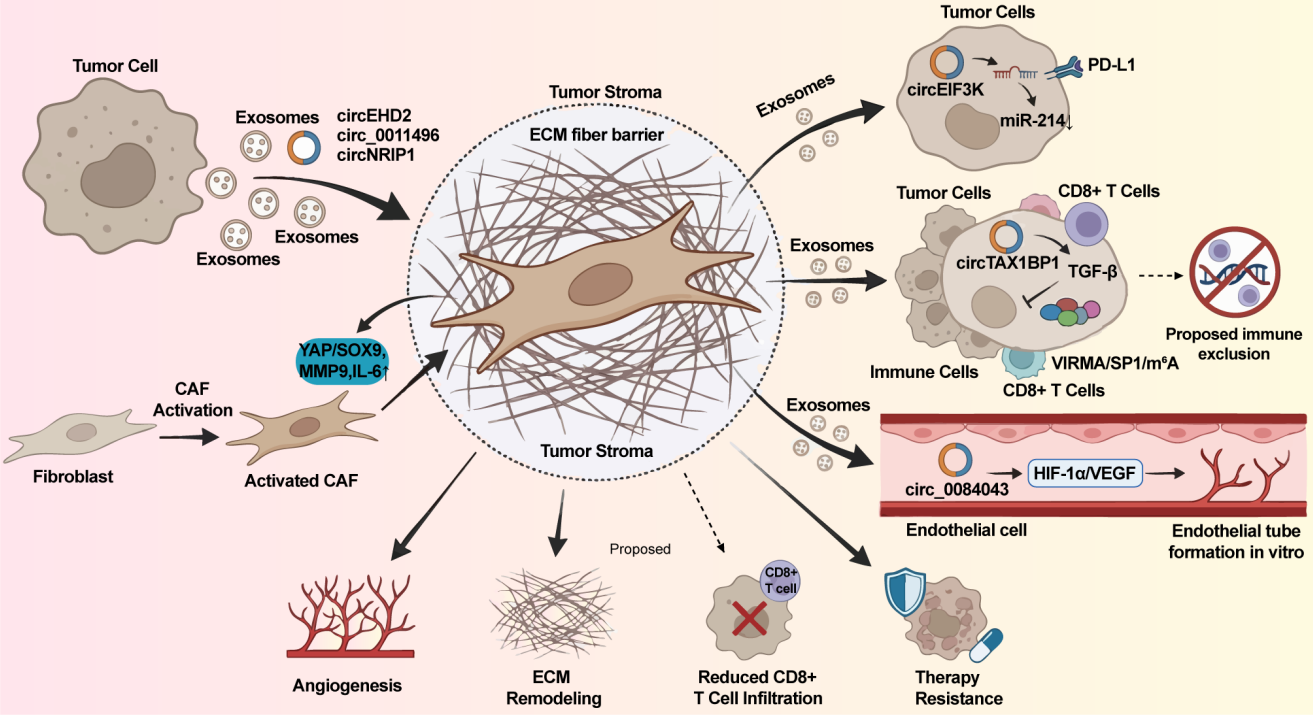

Figure 3. Bidirectional exosomal circRNA communication between tumor cells and cancer-associated fibroblasts shapes stromal remodeling, immune exclusion and therapy resistance. Schematic depiction of tumor cell and CAF communication mediated by exosomal circRNAs. Tumor-derived exosomal circRNAs can reprogram fibroblasts toward CAF-like states and promote inflammatory signaling. Activated CAFs remodel ECM and secrete factors that affect immune cell infiltration and checkpoint signaling. CAF-derived exosomal circRNAs can act on tumor cells to enhance immune evasion programs including PD-L1-associated pathways and can act on endothelial cells to promote angiogenesis. Stress conditions such as hypoxia or radiotherapy alter the CAF exosomal circRNA repertoire and link stromal remodeling to stemness and therapy resistance. Representative axes included are circEHD2-related fibroblast activation, circEIF3K-related PD-L1-associated regulation, circ_0084043-related angiogenesis signaling, and circTAX1BP1-related TGF-β program activation. circRNA, circular RNA; CAF, cancer-associated fibroblast; ECM, extracellular matrix; PD-L1, programmed death-ligand 1; HIF, hypoxia-inducible factor.

myofibroblastic CAFs released EV-associated circTAX1BP1 to tumor cells. CircTAX1BP1 recruited AARS2, increased VIRMA lactylation, stabilized SP1 messenger RNA through m^{6}A and raised tumor-cell TGF-β secretion. TGF-β then maintained the ITGA11-positive CAF state and further EV-associated circTAX1BP1 release (113). TGF-β-responsive fibroblast programs in other tumor models restrict T-cell entry and reduce PD-L1 blockade activity (25). In this CRC system, however, CD8$^+$ T-cell position and ICI response were not measured. CircTAX1BP1 may therefore sit upstream of a stromal condition that restricts T-cell access, with the immune step remaining to be tested in the same model.

Interventions at the fibroblast source or the delivered RNA act at several points in this communication. Matrine reduced CAF EV-associated circSLC7A6 through CXCR5 and lowered CRC-cell migration and invasion (114). Asparagine-glycine-arginine (NGR)-modified CAF-derived EVs targeted tumor vasculature, induced ferroptosis and reduced osteosarcoma chemoresistance, although the therapeutic material was engineered and was not a naturally transferred circRNA (115). In HCC, CAF EV-associated circZFR activated STAT3-NF-κB signaling during cisplatin resistance, while hepatic stellate cell EV-associated circWDR25 regulated ALOX15 and epithelial-mesenchymal transition (116,117). These endpoints concern chemotherapy response and tumor behavior. Their connection to ICI activity requires combination experiments in immunocompetent models. For circEIF3K, the measured endpoints were CRC-cell PD-L1 and endothelial tube formation through miR-214, without T-cell entry or ICI response (24). Fibroblast remodeling can therefore precede immune exclusion, yet proximity alone does not establish transfer or lymphocyte suppression. A direct test would locate the circRNA-producing cell, the receiving CAF or tumor cell and CD8$^+$ T cells in the same tissue, then perturb the circRNA while measuring matrix organization, T-cell access and treatment response.

7. From T-cell exhaustion to checkpoint upregulation: Coordinated immune evasion driven by exosomal and intracellular circRNAs

T-cell dysfunction can arise through direct RNA transfer into T cells, checkpoint regulation within tumor cells, reduced lymphocyte infiltration or expansion of suppressive T cells. These outcomes originate in different cells and are defined by different experimental endpoints. Exhaustion requires loss of proliferation, cytokine production or cytotoxicity together with sustained inhibitory receptors. Reduced T-cell abundance describes infiltration and does not establish delivery to T cells. Direct transfer into T cells has been measured in several tumor models. NSCLC-derived EV-associated circUSP7 entered CD8$^+$ T cells and regulated miR-934 and SHP2, reducing cytokine secretion, perforin, granzyme B and anti-PD-1 activity (15). HCC-derived EV-associated circCCAR1 entered activated CD8$^+$ T cells, bound PD-1 protein, reduced its ubiquitination and prolonged its half-life (14). Bladder cancer-derived

EV-associated circTRPS1 was linked to miR-141-3p, GLS1, redox regulation and T-cell exhaustion, although several metabolic steps were measured within tumor cells (16). In GC, EV-associated circFXR1 entered tumor cells and $CD8^+$ T cells, increased PD-L1 and mTOR signaling and reduced T-cell effector function during anti-PD-1 treatment (118). By comparison, other EV-associated circRNAs alter tumor or myeloid cells upstream of T-cell infiltration. In PDAC, circGANAB moved among tumor cells, reduced the stability of interacting RNAs and reduced $CD4^+$ and $CD8^+$ T-cell infiltration during anti-PD-L1 treatment (119). T-cell uptake was not measured. In acute myeloid leukemia, EV-associated circRNA-001264 induced M2-like macrophages and increased PD-L1, linking a myeloid recipient to checkpoint expression (120). These processes can reduce T-cell access or function without direct circRNA activity inside T cells.

Tumor-intrinsic circRNAs regulate PD-L1 through recurring miRNA-dependent routes. In NSCLC, circ_0001006 acted through miR-320a and PD-L1, while circRNA-002178 increased PD-L1 in LUAD cells and PD-1 in cocultured T cells (121,122). CircCHST15 regulated miR-155-5p, miR-194-5p and PD-L1, whereas circ_0101675 acted through miR-607 and PD-L1 (123,124). hsa_circ_0000190 increased soluble PD-L1, and circ_0010235 acted through miR-636 and PD-L1 in lung cancer (125,126). All routes reach a checkpoint endpoint but differ in the circRNA, miRNA and form of PD-L1 measured. Within tumor cells, treatment context further changes the route to checkpoint expression. Circ_0014235 regulated miR-146b-5p, YAP and PD-L1 during gefitinib resistance, while circ_0068252 regulated miR-1304-5p and PD-L1 during cisplatin resistance in NSCLC (127,128). CircCORO1C increased PD-L1 through NF-κB in HCC, and circ_001678 linked miR-326 and ZEB1 with the PD-1/PD-L1 pathway in NSCLC (129,130). These tumor-cell processes do not by themselves show T-cell uptake or resistance to an ICI. Checkpoint regulation can be connected to T-cell function only when coculture or treatment experiments are included. A comparable tumor-cell route occurs in PDAC, where circ_0046523 regulated miR-148a-3p and PD-L1 within tumor cells (131). This finding concerns checkpoint regulation in the producing cell and does not establish EV-mediated transfer or direct activity in T cells.

miRNA-dependent routes account for only part of tumor-cell checkpoint regulation. In BC, hsa_circ_0067842 regulated HuR, CMTM6 and PD-L1 stability, while circGSK3β linked miR-338-3p, PRMT5 and H3K4 trimethylation to PD-L1 transcription (132,133). CircNF1 regulated PD-L1 through two routes in ESCC, and m^6A-modified circSLCO1B3 regulated HOXC8 and PD-L1 in iCCA (134,135). CircRHBDD1 increased PD-L1 through IGF2BP2 in GC, while circ_0136666 regulated PRKDC and PD-L1 phosphorylation through miR-375 (136,137). These mechanisms place the checkpoint change inside tumor cells and should remain distinct from direct T-cell reprogramming. The direction of checkpoint regulation also differs among circRNAs. In GC, circ_0000372 increased PD-L1 through miR-488-3p, whereas circ_0000372 depletion reduced PD-L1, cell viability and immune escape (138). In CRC, circ_0007422 depletion reduced PD-L1 through miR-1256, while hsa_circ_0004872 reduced PD-L1 and immune escape in meningioma cells (139,140). CircPCBP2 increased stemness, chemoresistance and PD-L1 through miR-33a and miR-33b in diffuse large B-cell lymphoma (141). Epstein-Barr virus circBART2.2 increased PD-L1 in nasopharyngeal carcinoma, while circularized E7 RNA was assessed with GLUT1 and PD-L1 in anal squamous cell carcinoma (142,143). Direction and cellular setting must therefore be stated for each checkpoint-associated circRNA. Beyond checkpoint abundance, tumor-intrinsic circRNAs can change $CD8^+$ T-cell infiltration or response to checkpoint treatment. In bladder cancer, a circMGA-HNRNPL complex regulated $CD8^+$ T-cell infiltration and immunotherapy response (144). CircZMIZ1 depletion increased $CD8^+$ T-cell activity in HCC, while circATAD2 regulated IGF2BP3, m^6A and PD-L1 during immune escape in BC (145,146). CircAATF was linked to anti-PD-L1 treatment in gallbladder carcinoma, and m^6A-modified circIGF2BP3 reduced $CD8^+$ T-cell responses by promoting PD-L1 deubiquitination in NSCLC (147,148). Hypoxia-associated circPRDM4 increased HIF-1α and PD-L1 in HCC, while circ-Keratin 6c acted through miR-485-3p and PD-L1 in CRC (149,150).

Reduced effector immunity can also follow expansion of suppressive T cells. HCC-derived EV-associated circGSE1 entered T cells and activated a miR-324-5p-TGFBR1-Smad3 process that increased $FOXP3^+$ regulatory T cells (Tregs) and metastasis (151). In CRC, hsa_circ_0136666 regulated miR-497 and PD-L1 during Treg-mediated immune escape (152). hsa_circ_0069313 acted through miR-325-3p and FOXP3 in oral squamous cell carcinoma cells and Tregs (153). m^6A-modified circQSOX1 increased glycolysis and intratumoral Tregs and reduced anti-CTLA-4 activity in CRC (154). In the aforementioned study, the treatment endpoint was CTLA-4 blockade. Therefore, it should not be generalized to PD-1 therapy. Other tumor-cell circRNAs alter immune escape without direct transfer into T cells. CircNDUFB2 promoted IGF2BP protein degradation and activated antitumor immunity in NSCLC, while circFAM13B reduced glycolysis through IGF2BP1 and PKM2 and increased bladder cancer sensitivity to immunotherapy (155,156). In HCC, circSOD2 acted through miR-497-5p and ANXA11 during tumor progression and anti-PD-1 resistance (157). In iCCA, circHMGCS1-016 regulated CD73 and galectin-8 through miR-1236-3p (158). These pathways affect tumor metabolism, RNA stability or extracellular suppression and can converge on T-cell activity without using the same molecular route. The remaining EV-associated circRNAs link tumor metabolism or growth to treatment response without a direct lymphocyte endpoint. NSCLC EV-associated circSHKBP1 increased PKM2-dependent glycolysis, while macrophage EV-associated hsa_circ_0004658 reduced HCC progression through miR-499b-5p and JAM3 (159,160). CircSCUBE3 reduced anti-PD-L1 activity in GC, and circFAT1 increased stemness and immune escape through STAT3 (161,162). CircHMGB2 and circCELF1 promoted immunosuppression and anti-PD-1 resistance in lung cancer through CARM1 and EGFR-related routes (163,164). Circ-HSP90A increased stemness and checkpoint signaling in NSCLC, while another NSCLC circRNA increased anti-PD-1 resistance through miR-30a-5p and SOX4 (165,166). Tumor-cell state was linked to treatment response, whereas direct transfer to T cells was not established.

8. Translational paths and methodological rigor in exosomal circRNA research

Circulating assays, endogenous inhibition and engineered delivery begin with different measurable entities. A biomarker assay relates RNA abundance to a defined clinical state. Sequence-specific inhibition tests whether lowering a circRNA changes a tumor or immune phenotype. An engineered product delivers a controlled RNA sequence to a selected tissue or cell. One route does not establish the others. Among these paths, biomarker development begins with variation across biofluids and cancer types. Plasma EV profiling identified circRNA patterns in GC, while an exosomal circRNA-miRNA-messenger RNA network was assembled in BC (167,168). A cross-biofluid analysis further mapped circRNA patterns across EV populations (169). Two international melanoma cohorts identified a five-circRNA signature associated with overall survival and progression-free survival among patients receiving anti-PD-1 monotherapy (170). These profiles can define candidates, whereas clinical prediction requires pretreatment sampling, a fixed assay, a prespecified threshold and a treatment-specific endpoint in an independent prospective cohort. Total particle concentration and circRNA abundance per particle should be measured separately.

Therapeutic manipulation then divides into RNA delivery and sequence-directed inhibition. Naturally secreted EVs can be engineered for treatment. EV-mediated circDIDO1 delivery reduced GC growth through miR-1307-3p and SOCS2 (171). A gelatin methacryloyl (GelMA) hydrogel carrying circNEFM-engineered EVs reduced glioma growth, while circPRKD3-loaded EVs altered glioblastoma growth and the local environment through STAT3 signaling (172,173). These systems require control of particle composition, loading distribution, tissue localization, batch potency and repeated-dose toxicity. Their performance does not determine the physiological dose of the corresponding endogenous EV-associated circRNA. By contrast, sequence-directed inhibition uses a different product and target. pH-responsive niobium carbide nanosheets delivered circPUM1 small interfering RNA (siRNA) in ovarian cancer, and nanoparticles targeting circTNK2 restored tamoxifen sensitivity and increased NK-cell activity in estrogen receptor-positive BC (174,175). Back-splice-junction antisense oligonucleotides or siRNAs should be tested against the linear host transcript, other circular isoforms and normal tissues. Target engagement should be measured in the tumor and the recipient cell implicated by the biological model.

CircRNA vaccines form a third path because circular topology extends antigen or therapeutic protein expression. Circular RNA vaccines produced antitumor activity in resistant tumor models and induced potent T-cell responses (176,177). A circular RNA neoantigen vaccine was developed for HCC, while lipid nanoparticle composition altered vaccine delivery and the T-cell response (178,179). A DC vaccine carrying circRNA increased antitumor immunity when combined with low-dose gemcitabine in pancreatic cancer (180). Local circILNb expression delivered IL-15 and an anti-PD-L1 nanobody in cold tumors (181). These platforms concern antigen or protein expression and remain separate from natural EV-mediated circRNA transfer. Within vaccine platforms, neoantigen selection and RNA manufacture determine activity. Circular RNAs can serve as a source of neoantigens, and artificial circRNAs have been used as miRNA-binding constructs and anti-PD-1 single-chain variable fragment expression platforms (182,183). An enhanced permuted intron-exon system improved production of therapeutic circRNAs (184). In 2026, a multi-neoantigen circRNA vaccine altered melanoma immune-cell composition and increased checkpoint-blockade activity (185). A lipid nanoparticle circRNA vaccine encoding NY-ESO-1 induced antigen-specific immunity and enhanced checkpoint-blockade activity in lung cancer models (186). These products require full sequence definition, removal of linear and double-stranded RNA, expression kinetics and innate immune testing. Circular RNA manufacture also supports transient programming of immune cells. Scarless circular mRNA produced chimeric antigen receptor T cells, while a circRNA platform generated DLL3-targeted chimeric antigen receptor T cells for small-cell lung cancer (187,188). A 2026 platform combined rapid receptor screening with circRNA-driven chimeric antigen receptor NK cells and IL-21 to resist antigen shedding in pancreatic cancer models (189). These approaches address receptor expression, cell manufacture and persistence. They do not model the uptake of a naturally secreted EV-associated circRNA (Table SIII).

Across these translational paths, methodological control determines whether a result can be assigned to a vesicle-associated RNA. Blood collection tubes, processing delay, centrifugation and storage can change particle and RNA measurements. EV preparations should be assessed for morphology, size, particle concentration, EV-enriched proteins, negative markers and co-isolated material. RNase treatment with and without membrane disruption distinguishes protected RNA from externally associated RNA. Donor-cell depletion, particle-normalized exposure, increased intact circRNA in the recipient and reversal of the recipient phenotype connect the measured response to EV-mediated transfer. Absolute dose, tissue distribution and recipient-cell delivery then determine whether the experimental exposure can occur *in vivo* (Fig. 4 and Table SIV).

9. Discussion

EV-associated circRNAs can reduce cytotoxic immunity through direct activity in NK cells and $CD8^+$ T cells, through macrophages that subsequently suppress T cells and through tumor or stromal states that restrict immune-cell access. These routes converge on reduced effector function or treatment response, yet the point at which the circRNA acts differs. A transferred RNA inside an immune cell supports a different conclusion from a tumor-intrinsic circRNA that changes PD-L1 or an EV-associated circRNA that remodels fibroblasts. Keeping the donor, EV population, recipient and intracellular process explicit prevents these processes from being merged into one mechanism. This separation also explains why the direction of regulation changes with donor state, recipient identity and tissue site. Hypoxia changes circRNA production in tumor cells and CAFs. Macrophage-derived EVs can return circRNAs or other RNAs to tumor cells. Tumor-intrinsic circRNAs can either increase or reduce NK-cell recognition. These differences do not represent a uniform dual effect of

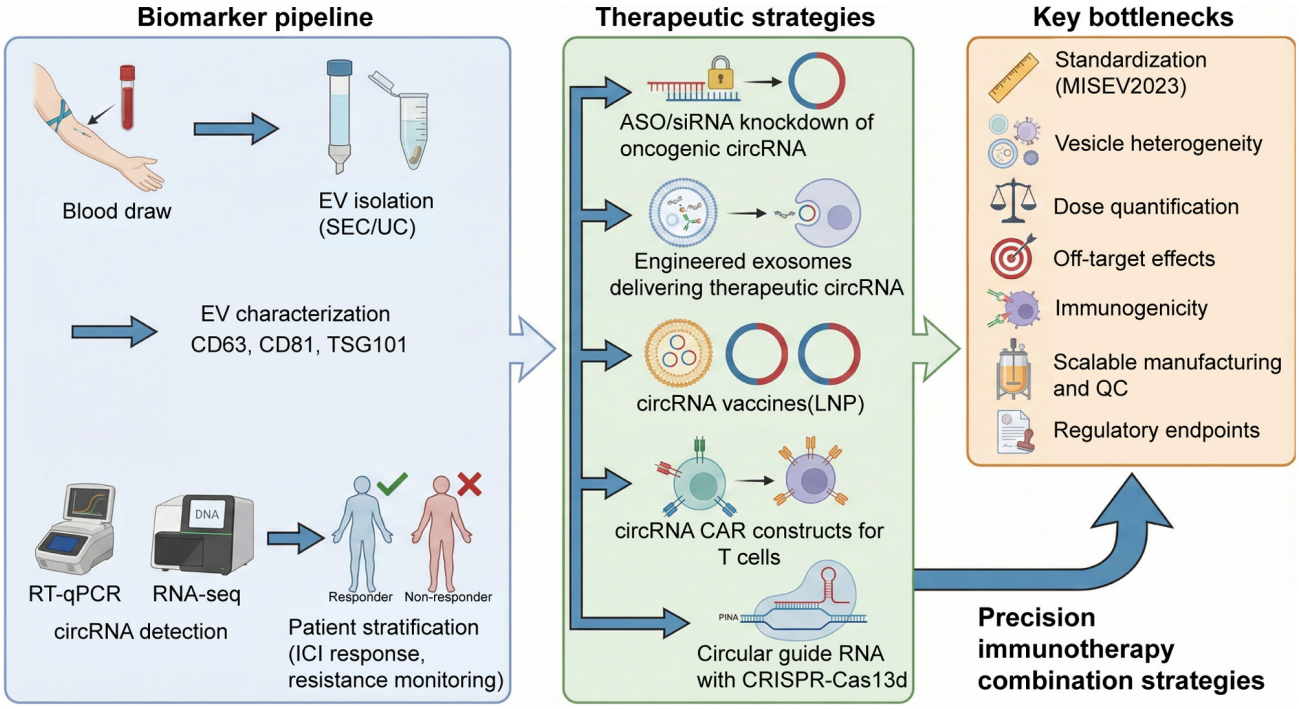

Figure 4. Translational roadmap for exosomal circRNAs from biomarker development to therapeutic intervention and quality control requirements. Conceptual roadmap for clinical translation of exosomal circRNA research. The left module outlines a biomarker pipeline from biospecimen collection through EV isolation and characterization to circRNA quantification and clinical association with immune status or treatment response. The middle module summarizes therapeutic strategies including antisense oligonucleotide-mediated knockdown of oncogenic circRNAs, engineered exosome delivery of therapeutic circRNAs, circRNA vaccines, and circRNA-based cellular engineering. The right module highlights key barriers that must be addressed for clinical readiness, including standardization of EV workflows, vesicle heterogeneity, dosing and biodistribution, off-target effects, immunogenicity assessment, scalable manufacturing and quality control. ASO, antisense oligonucleotide; CAR, chimeric antigen receptor; Cas13d, CRISPR-associated protein 13d; circRNA, circular RNA; CRISPR, clustered regularly interspaced short palindromic repeats; EV, extracellular vesicle; ICI, immune checkpoint inhibitor; LNP, lipid nanoparticle; QC, quality control; RNA-seq, RNA sequencing; RT-qPCR, reverse transcription-quantitative PCR; SEC, size-exclusion chromatography; siRNA, small interfering RNA; UC, ultracentrifugation.

circRNAs. They arise because distinct molecules act in different cells and alter different molecular targets. The same immune lineage can therefore acquire different states under different exposure and treatment conditions.

A one-step connection may nevertheless link circRNA-dependent stromal remodeling to immune-cell access. A circRNA that maintains a TGF-β-dependent myofibroblastic CAF state may reduce T-cell entry when that fibroblast state is already known to form a matrix associated with T-cell exclusion. This connection remains a hypothesis until circRNA transfer, fibroblast state and T-cell position are measured together. A further connection to ICI response requires treatment in the same model. The same boundary applies when macrophage polarization is linked to metastatic growth or when tumor-cell PD-L1 is linked to T-cell exhaustion. miRNA regulation remains common, although binding assays and reporter rescue establish compatibility rather than quantitative competition. The delivered circRNA must reach the same intracellular compartment as the miRNA and contribute enough binding sites relative to the full target pool. RBP complexes, protein modification, RNA destabilization and translation avoid this particular constraint but introduce others. They require mapped interaction sites, full-length isoform identification, site-specific perturbation or peptide rescue. A back-splice junction alone cannot distinguish molecules with different internal sequences and functions.

EV heterogeneity alters the exposure that precedes every intracellular mechanism. Bulk measurements can combine particles with different surface proteins, tissue distributions and RNA contents. They can also include material outside EVs. Single-EV methods now resolve molecular variation across particles, but current datasets do not provide a general copy number for individual cancer-associated circRNAs. Quantitative transfer experiments should therefore measure the fraction of positive particles, copies per positive particle, particles encountered by each recipient cell and cytosolic delivery efficiency. These values can determine whether an observed phenotype is compatible with exposure in tissue.

Clinical development should proceed along three separate paths. Biomarker development needs treatment-specific cohorts, fixed assays and independent prospective validation. Endogenous inhibition needs sequence specificity, recipient-cell rescue and combination testing with the intended therapy. Engineered circRNA or EV products need controlled composition, tissue distribution, target engagement, potency and repeated-dose safety. A result that reduces tumor growth or metastasis does not establish ICI sensitization until both treatments are tested together in an immunocompetent model. Across all three paths, the next experiments should place molecular transfer within tissue structure. Spatial RNA detection can identify circRNA-producing cells, recipient macrophages or CAFs and nearby $CD8^+$ T cells in the same

specimen. Perturbation can then test whether circRNA loss changes the recipient state and T-cell position. Serial samples from ICI-treated patients can determine whether circulating EV-associated circRNAs precede response, follow tumor burden or reflect immune-cell composition. Combined with absolute measurement and full-length sequencing, these measurements can distinguish a circulating marker from a transferred regulator and a transferred regulator from a treatment target.

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Availability of data and materials

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Authors' contributions

WZ, BZ and SZ conceptualized the study. NC, LG, YD, HS, XL, JS, LL, ZJ, LW and XH conducted investigation. WZ, YD, HS and XL performed visualization (figures and tables). WZ, NC and LG wrote the original draft. BZ, SZ and WZ wrote, reviewed and edited the manuscript. BZ and SZ supervised the study and acquired funding. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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