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Potential Value and Mechanistic Basis of Tumor-Derived Exosomes in Postoperative Cancer Recurrence Monitoring

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Abstract. Postoperative recurrence is an important aspect of clinical management of solid tumors due to the presence of minimal residual disease which cannot be detected by conventional surveillance techniques. Although circulating tumor DNA can be viewed as one of the most potent methods of recurrence monitoring, it does not give much information on interactions between the tumor and microenvironment that have a significant impact on the course of relapsed tumors. The tumor-derived exosomes, small extracellular vesicles containing various biomolecules such as RNAs, proteins and DNA fragments, are a promising alternative platform. The review provides a systematic overview of the biology of tumor-derived exosomes, their isolation technologies, and their role in some of the main recurrence-related mechanisms, such as pre-metastatic niche creation, immune escape through exosomal PD-L1, angiogenesis, therapy resistance, and tumor dormancy. We also provide a summary of clinical findings that back up the use of exosomal RNA, protein and EV-DNA markers in predicting postoperative recurrence in various types of cancer. Though promising, there are still major obstacles, such as methodological heterogeneity, absence of standardized processes, and inadequate prospective validation. Harmonization of pre-analytical protocols, well-structured multi-center cohort studies, and mechanistic biomarker selection will be needed in future translations. Altogether, tumor-derived exosomes present a biologically sound and technologically practical opportunity to improve postoperative surveillance, and may be used to enhance current liquid biopsy methods.

Keywords: postoperative recurrence, minimal residual disease, liquid biopsy, biomarker

1. Introduction

The recurrence of solid tumors following surgery has been one of the most significant clinical challenges in the field due to the hidden nature of minimal residual disease (MRD) which is not controlled in the perioperative period. The liquid biopsy and more specifically, the circulating tumor DNA (ctDNA) have revolutionized postoperative surveillance through the possibility of detecting an early relapse and stratifying risks [1]. Nevertheless, methods based on ctDNA have disadvantages: detectability depends on tumor burden and shedding dynamics, as well as they give little information about the interaction between tumor and microenvironment, including immunosuppression, angiogenesis and the development of pre-metastatic niche, which are important steps towards recurrence.

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Exosomes released by tumors, which are small extracellular vesicles (30-150 nm) containing a wide variety of biomolecules, such as RNAs, proteins, and even DNA fragments, can serve as a strong complementary platform. They are actively released by living cells, have dynamic cellular states, and functionally engage in some of the main processes related to recurrence, such as immune escape and niche training [2]. Exosome tests are less sensitive than ctDNA, but they give more information on the biology of the cells, and fixate the analytes in the circulation. Initial trials show good recurrence prediction results of AUC of ~0.8 in various cancers, indicating some complementarity to clinical staging and ctDNA status [3].

Although the interest is growing fast, there are still significant obstacles such as heterogeneous methods, the lack of standardization and inadequate prospective validation. Clinical implementation of exosome biomarkers will require harmonized processes, stringent analytical validation, and well-organized multi-center trials

2. Biological features for tumor-derived exosome

2.1. Exosome biogenesis and secretion mechanisms

Exosomes are derived by the endosomal system: inward budding of the limiting membrane of early/late endosomes generates intraluminal vesicles (ILVs) which accumulate inside MVBs; MVBs merge with plasma membrane releasing ILVs as exosomes into the extracellular region. The pathway may intersect with endosomal sorting complexes required for transport (ESCRT)-dependent and ESCRT-independent pathways, and be altered by lipid microdomains. In a groundbreaking paper it was demonstrated that ceramide facilitated the formation of ILVs within MVBs and neutral sphingomyelinase inhibition decreased exosome release, which is direct proof of ceramide-induced, ESCRT-independent contribution to exosome formation [4].

Since exosome secretion plays a role in tumor-host communications, pharmacological alteration of exosome biogenesis and secretion has played an important part in mechanistic models. Examples include using compounds like GW4869 (neutral sphingomyelinase inhibitor), which is commonly used to inhibit the release of exosomes, but it may be sensitive to cell type and pathway dependence, with inhibition also having a more general effect on lipid signals. Therefore, the approaches to inhibiting exosomes are largely experimental, and the translational applicability of these approaches to the prevention of recurrence has not been determined.

In terms of its nomenclature and rigour, it is important to appreciate the fact that most of the so-called exosomes in the literature are defined in practice as small EV fractions, not as vesicles that have been shown to be the result of only MVBs. The International standards focus on precise language (EVs; small EVs), and demand various orthogonal characterization stages prior to the claim that can be made about the identity or function of an exosome.

2.2. Molecular composition of exosomes

Exosomes are membrane and luminal biomolecules that are a partial representation of their parent cell. Tetraspanins (such as CD9, CD63 and CD81), proteins involved in MVB formation (such as TSG101, ALIX), heat shock proteins and cell-type-specific surface antigens are canonical exosomal protein enrichments. Exosomes have also been shown to carry RNAs (miRNA, mRNA, lncRNA, circular RNA), lipids involved in maintaining membrane stability, and DNA pieces (ev-DNA) that have been found in various settings. Since none of the single markers is completely specific, the

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characterization generally needs to be performed using a panel approach: positive markers, negative/contamination markers, and evaluation of the particle size distribution and morphology.

The presence of EV-related double-stranded DNA (dsDNA) has been reported in tumors and suggested as a possible biomarker substrate. One example report revealed dsDNA in exosomes and pointed to the possibility of detecting cancer using exosomal DNA analysis. However, EV-DNA analysis needs precise regulation of confounding signals due to co-isolated free DNA and DNA attached to vesicle surfaces; enzymes (e.g., DNase), and checking the integrity of vesicles are also sometimes used to substantiate claims that the DNA is luminal, and vesicle-bound, and not contaminants [5].

2.3. Isolation and analytical technologies for exosomes

Strong biomarker development needs isolation and detection techniques which are reproducible, scalable and fit-for-purpose in a postoperative surveillance environment. In practice, workflows tradeoff yield to purity. One commonly used procedure is differential ultracentrifugation, which can produce very large particle yields but has the potential to co-isolate protein aggregates and lipoproteins especially when using plasma. Conversely, SEC could be used to obtain higher purity by eliminating soluble protein contaminants, but with the drawback of lower vesicle output and increased handling steps. Comparative plasma research demonstrated that SEC-based isolation produced exosome markers with less albumin contamination than ultracentrifugation, which indicates that there are practical trade-offs between purity and recovery.

Enrichment of target can be added to EV isolation of bulk in order to enhance specificity towards tumor-associated subpopulations. Immunoaffinity capture (e.g. against tumor-associated surface proteins) will enrich relevant vesicle subsets following SEC purification, however, it can cause bias (towards marker-positive subpopulations), decrease overall recovery and make quantitative comparison between cohorts challenging. These limitations are particularly applicable to postoperative MRD surveillance, as the signals may be low.

The most feasible surveillance-driven workflow, which is based on the current guideline reasoning and typical clinical limitations, may imply the following measures: EDTA plasma sampling is feasible instead of serum; rapid processing with standardized centrifugation to eliminate cells and platelets; uniform storage and freeze-thaw management; and post-extraction EV isolation using SEC and/or ultracentrifugation depending on the target analyte. The analytical platforms must be able to have adequate external controls, internal controls and negative controls and quantify both particle and cargo in order to ensure interpretability. It is suggested that reporting be transparent, such as depositing parameters of methodology into community resources.

A variety of analytical modalities are typically used. Reverse transcription quantitative PCR (RT-qPCR), ddPCR and next-generation sequencing are very common to use with nucleic-acid cargo. The absolute or almost absolute quantification by large-scale reaction partitioning provides a sensitive detection of rare alleles and accurate estimation of copies in complex backgrounds, which is the principle behind its utility on low abundance signals after surgery.

Sophisticated technology like nano-flow cytometry allows detecting EV-associated DNA at a single-vesicle level with a high resolution to provide more information on EV heterogeneity and cargo distribution in particle characterization and single-vesicle analysis (Figure 1).

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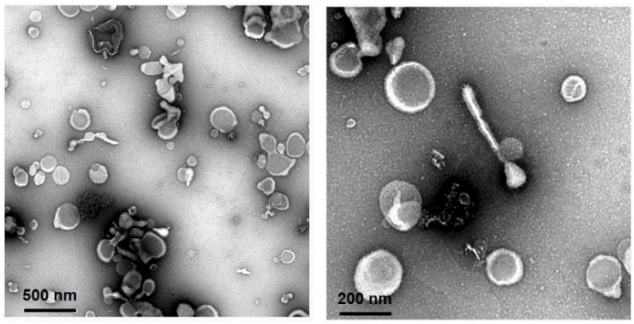

Figure 1. Nano-flow cytometry enables single-vesicle detection of EV-DNA, revealing heterogeneity in DNA distribution among extracellular vesicles

One of the latest studies reported a lab-made nano-flow cytometer (nFCM) able to detect individual EVs as low as ~40 nm and allowing single-vesicle EV-DNA analysis, as well as depicted the fact that extracellular DNA and non-vesicular DNA-linked elements could be highly present in EV preparations based on separation and processing [6]. Lastly, strict and open reporting is vital towards reproducibility in the EV field, with community based platforms like EV-TRACK being created to standardize experimental reporting and enhance the comparability of data (Figure 2) [7].

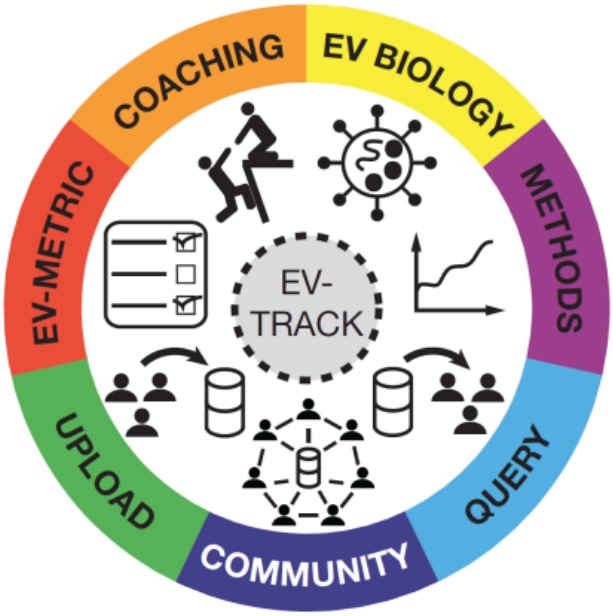

Figure 2. EV-TRACK platform promotes standardized reporting and improves reproducibility in extracellular vesicle research

3. Mechanistic roles of tumor-derived exosomes in postoperative recurrence

3.1. Tumor microenvironment remodeling and the pre-metastatic niche

Recurrence is not merely an effect of residual malignant cell propagation but also indicates supportive environmental factors in local and distant microenvironment that allow outgrowth, invasion, and immune escape. Exosomes derived by tumor play a role in the creation of pre-

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metastatic niche through the transfer of proteins and nucleic acids to organ-resident cells, as well as by directing the inflammatory response, extracellular matrix remodeling and cell recruitment.

One of the pioneering works showed that exosomal integrin expression patterns play a role in organotropic metastasis: tumor exosomes tend to fuse preferentially with resident cells in the future metastatic organs, and particular integrins (e.g., α6b4/alpha6beta1 to lungs, alpha v beta5 to liver) correlated with destination specificity; targeting integrins decreased exosome uptake and metastatic load. It gives a mechanistic framework of how exosomes predispose particular organs to recurrences patterns [8].

Pancreatic cancer exosomes have demonstrated to trigger the pre-metastatic niche formation through their interactions with the hepatic cells and subsequent promotion of pro-fibrotic and inflammatory pathways that promote metastatic colonization and proliferation. These niche-conditioning mechanisms are conceptually compatible with the postoperative recurrence, wherein clinically occult residual disease could take advantage of already-conditioned tissues to develop detectable relapse.

3.2. Immune regulation and angiogenesis

Exosomes containing tumor-derived proteins are capable of altering the activity of the immune surveillance system by providing the immunoregulatory proteins that inhibit the stimulation of T cells, one of which is the exosomal PD-L1 and has become an important mediator of systemic immune escape (Figure 3). One of the main mechanisms of systemic immune inhibition has been identified as exosomal programmed death-ligand 1 (PD-L1; encoded by CD274). In a mechanistic experiment, reduction of exosomal PD-L1 discharge led to systemic and persistent anti-tumor immunity and immunity memory, implying that exosomal PD-L1 may play a significant role in the process of immune escape and that this inhibition might be used to boost immune regulation. Such observations imply that, in the postoperative environment, PD-L1-bearing exosomes might facilitate the immune escape of cryptic MRD and thus facilitate the recurrence [9].

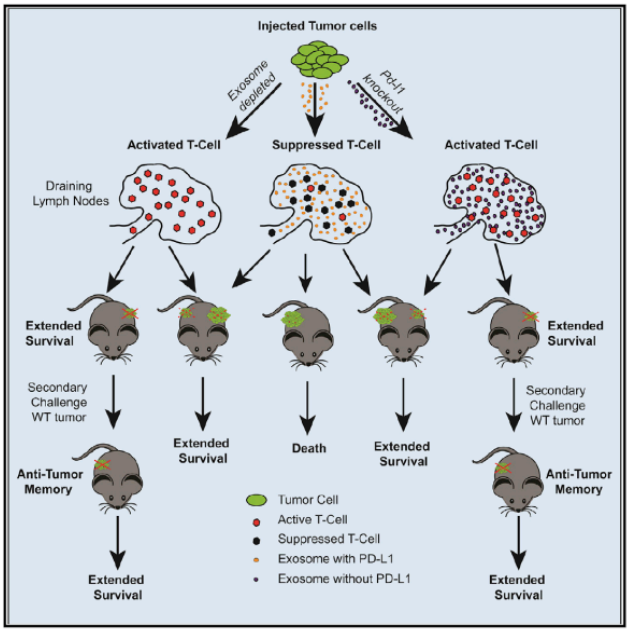

Figure 3. Exosomal PD-L1 suppresses T cell activity and promotes systemic immune evasion, facilitating tumor progression and recurrence

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The development of recurrent lesion beyond minimal size also requires angiogenesis as an essential component. Tumor exosomes have been found to reprogram endothelial cells and provide them with angiogenic factors which in turn supports both neovascularization and metastatic growth. Exosome-mediated vascular effects are directly supported by exosomes that promote angiogenesis through functional reprogramming of endothelial cells in head and neck squamous cell carcinoma (HNSCC) tumors, directly addressing the role of exosomes in recurrence biology [10].

3.3. Therapeutic resistance and tumor dormancy

Even following a supposedly curative surgery and perioperative intervention residual lesions may be present due to selective pressure. Exosomes are involved in therapy resistance through their transfer of drug transporters, anti-apoptotic messages and resistance-related miRNAs to recipient tumor or stroma cells.

Exosomal transfer of microRNA-21 (miR-21) by tumor associated macrophages was demonstrated to induce cisplatin resistance in gastric cancer, an example of how the exosome-mediated communication between stroma and tumor can directly alter the response to therapy. Since miR-21 can also hit tumor suppression pathways (such as PTEN and PDCD4 in many situations), exosomal miR-21 and its networks are likely to help residual malignant cells survive adjuvant therapy, thus enhancing the probability of a relapse.

Tumor dormancy is another relapse route: scattered or remaining tumor cells may enter less proliferative phases, escaping treatments aimed at dividing cells, and then revive again upon alteration of microenvironmental indications. The involvement of exosomal miRNAs has been suggested to induce quiescence and drug resistance in subpopulations of cancer cells. An example is that breast cancer cells were found to prime mesenchymal stem cells (MSCs) to produce exosomes containing high levels of miR-222/223, which induced quiescence and led to drug resistance; targeting such miRNAs with therapy has been studied as a treatment to dormant cells. These findings indicate that there is a biologically feasible function of exosomes in promoting MRD pools capable of eliciting late recurrence [11].

4. Clinical applications of exosomes in postoperative recurrence monitoring

4.1. Exosomal RNA biomarkers

The intensive research on exosomal miRNAs to predict recurrence is due to their stability in circulation, relative ease of analysis and the ability to indicate both intrinsic and extrinsic tumor biology and microenvironmental biologic programs.

A decrease in serum exosomal miR-4772-3p has been proposed as a prognostic biomarker of recurrence in stage II/III colon cancer and the analysis of receiver operating characteristics gave a value of 0.72 to the area under the curve to predict recurrence in the cohort reported. The given example shows that it is possible to use exosomal miRNA signals to stratify the risks of patients before and after surgery [8].

A pre-treatment exosomal miRNA panel was created as a predictor of recurrence following surgery in patients with pancreatic ductal adenocarcinoma (PDAC) by a multicohort study. The trained six-exosomal-miRNA risk model differentiated recurrence with AUC of 0.81 in the training cohort and AUC of 0.78 in an independent validation cohort, and was additionally validated in a post-neoadjuvant cohort. This is very similar to the performance profile often desired of clinically

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actionable stratification tests and it also implies that exosomal miRNA signatures can be used to predict relapse risk before curative treatment [12].

Plasma exosomal miR-21 and miR-4257 were found to be recurrence-related biomarkers in NSCLC and tested on a more extensive sample, where increased values correlated with decreased disease-free survival in multivariate analyses. It demonstrates the extension of the method to other than gastrointestinal tumors and lends support to its applicability to solid tumors in general.

Other than miRNAs, exosomal lncRNAs and circular RNAs are becoming new potential sources of relapse markers. In surgically treated NSCLC, serial examination of extracellular vesicle HOTTIP (HOXA distal transcript antisense RNA) revealed postoperative elevations in relapsed patients; the initial postsurgical sample ratio was found to be predictive of recurrence with published high sensitivity and specificity (study-specific operating characteristics). The present study is encouraging to a clinically desirable idea that regular follow-ups on EV-RNA levels may offer some early biochemical relapse indicators than imaging itself would, thus facilitating a quicker response [13].

The use of exosomal miRNA has been explored to predict postoperative hematogenous metastasis in gastric cancer. In one stage II/III cohort study, exosomal miR-379-5p and miR-410-3p were found to correlate with later hematogenous metastasis following surgery and poor progression-free survival was demonstrated, which supports the use of exosomal miRNAs as metastasis- and relapse-related markers in gastric cancer.

4.2. Exosomal protein and EV-DNA biomarkers

The protein cargo has its biological context that can add to the nucleic-acid biomarkers but would need to be meticulously designed into the assays to ensure that it does not interfere with the heterogeneity of the EVs and the plasma proteins co-isolated with them. Circulating exosomes positive for Glypican-1 (GPC1) have been cited as good biomarkers to detect cancers and monitor tumor load, which indicates the possible use of exosomal surface proteins as clinically useful markers. It is important to note that antibody-based capture strategies allow the selective enrichment and detection of tumor-derived exosomes through surface protein recognition, offering a practical platform towards their clinical application (Figure 4) [13]. Later works have challenged their applicability to different cohorts and platforms, however, this piece set a key precedent that exosomal surface proteins are measurable and clinically useful signatures especially when combined with other analytes to monitor postoperative patients [14].

Proteins with immunoregulatory properties transported by tumor exosomes could also be useful as biomarkers, particularly, if correlated to recurrence mechanistically. This is an example of exosomal PD-L1: since it is involved in the systemic immune suppression, it can be used to predict the ability of residual diseases to evade the immune system and can serve as an addition to ctDNA and exosomal RNA messages in relapse risk models.

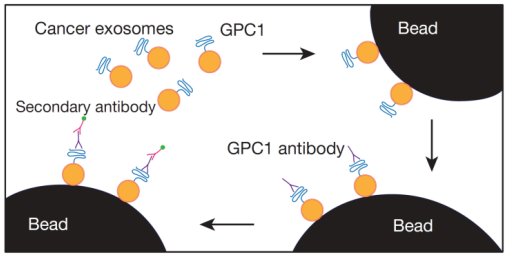

Figure 4. Antibody-based capture of GPC1-positive exosomes

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EV-DNA is also one of the other potentially informative substrates. Exosomal dsDNA has been proven and suggested to be a material associated with biomarkers. Theoretically, in postoperative monitoring, EV-DNA might supplement ctDNA due to its presence as protected DNA fragments and possibly distinct shedding kinetics. Nevertheless, technical issues related to EV-DNA are significant: the measurement of both co-isolated extracellular nucleic acids may confound them, and evidence indicates that DNA may position itself outside the vesicles or onto the surfaces of vesicles depending on the conditions used to isolate and treat them. The possibility of detecting EV-DNA and the heterogeneity and contamination hazards Single-vesicle analysis of nFCM reveals the potential of detecting EV-DNA and the heterogeneity and contamination hazards which need to be considered when validating assays.

In reporting tumor-related mutations, it is important to differentiate between gene-level changes (e.g., EGFR, TP53) and protein expression and to report whether mutations were found in EV-DNA, cell-free DNA, or both. Currently, EV-DNA mutation detection in postoperative recurrence surveillance is preliminary compared to ctDNA MRD detection and needs more prospective comparison with ctDNA, imaging and clinical outcomes.

4.3. Clinical evidence landscape

Most of the exosome biomarker studies on postoperative recurrence monitoring across tumor types are retrospective cohorts, small prospective observational, or case-control designs. The evidence levels generally match the early stages of biomarker development (analytical feasibility, exploratory discovery and preliminary validation), not the advanced clinical utility trials with pre-determined endpoints and decision impact analysis.

Critical concerns are heterogeneity of cohorts, timepoints of sampling, pre-analytic differences in processing (plasma versus serum, time to process, centrifugation and platelet removal), and different technology in isolation/detection processes that might significantly change recovered EV populations. These sources of variability make cross-study comparisons and meta-analytic synthesis difficult and may inflate apparent effect sizes due to lack of rigorous separation between discovery and validation.

The clinical usefulness of exosome biomarkers will probably be determined in comparison to existing practice, not in isolation [15]. In colorectal cancer, a case in point, the MRD status of ctDNA is extremely prognostic and can delineate highly risky subsets. Exosomes as biomarkers can be valuable because they can (i) indicate relapse risk when ctDNA is negative or indeterminate, (ii) provide mechanistic information (immune suppression, niche conditioning, resistance programs), and (iii) allow multi-analyte models of risk which combine EV-RNA, EV-protein and ctDNA to enhance performance and interpretation. It is important to demonstrate such additional value with clinical decision-making systems in a prospective manner, not retrospectively infer it through correlation alone.

5. Conclusions and outlook

Tumor-derived exosomes are a technologically and biologically attractive tool to monitor recurrence after surgery, especially exosomal miRNAs and lncRNAs. Current data confirms the idea that exosomal RNA signatures can be used to classify relapse risk and in certain tumor types and population groups have predictive metrics of performance close to those needed in order to move towards translation (e.g., recurrence-risk AUC values of about 0.8 reported in PDAC exosomal miRNA panel). Exosomes provide a mechanistic link between biomarker signals and the biology of

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recurrence, such as pre-metastatic niche formation, immune escape (especially through exosomal PD-L1), angiogenesis, therapy resistance and tumor dormancy.

However, to translate into standard follow-up pathways, one must move away the focus on biomarker discovery and instead engage in closely regulated validation and utility research. An important priority is pre-analytic and analytic standardization, i.e., standardized blood collection (ideally plasma with a specified anticoagulant), controlled processing time, constant platelet exclusion, and validated isolation methods with measured yields/purities. MISEV framework gives practical directions in defining, characterizing, and reporting EVs, whereas EV-TRACK offers a tangible route to the transparent disclosure of methodologies.

The next priority is the prospective multi-center cohort validation involving clinically relevant endpoints. The studies must predefine sampling schemes (perioperative baseline; early postoperative intervals; serial follow-up), specify the recurrence endpoints using standardized adjudication, and include direct comparison with ctDNA MRD and imaging assays. Ctdna studies in colorectal cancer offer an example of the application of MRD-driven risk stratification that can be implemented; similar designs can be applied to multi-analyte models that include extracellular vesicle-DNA and/or exosomal RNA/protein.

One other priority is mechanism-based selection of biomarkers. Integrating mechanistic priors, including immune suppression pathways (e.g., exosomal PD-L1), niche-conditioning (integrins), and resistance/dormancy (miRNA) programs, rather than simply using purely statistical signatures, could increase biological interpretability, decrease overfitting, and enhance cross-cohort robustness. These methods also provide better connections with actionable interventions (immunotherapy, anti-angiogenic approach, or escalation aimed at resistance).

Overall, tumor-derived exosomes have great potential as a supplementary tool to ctDNA in postoperative monitoring, however their implementation will rely on standardization of methods, strict evidence accumulation and verifiable improvement in clinical value in actual postoperative follow-up schemes.

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