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PERSPECTIVE

Exosome-Mediated Intercellular Communication in Tumor Microenvironment Remodeling

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ABSTRACT

Extracellular vesicles, and exosomes in particular, have moved over the past fifteen years from a presumed cellular waste-disposal mechanism to a recognised and mechanistically substantial channel of intercellular communication within the tumor microenvironment, capable of transferring proteins, lipids, and regulatory RNA species between tumor cells, stromal fibroblasts, endothelial cells and immune populations in ways that measurably influence tumor progression, immune evasion and metastatic niche formation. This perspective synthesises the current mechanistic evidence for exosome-mediated remodeling of four microenvironmental compartments, cancer-associated fibroblast activation, tumor angiogenesis, immune cell reprogramming, and pre-metastatic niche establishment at distant organ sites, and evaluates where the field's mechanistic claims rest on solid experimental ground versus where correlative or in-vitro-only evidence still outpaces causal demonstration in intact tumor systems. We argue that exosomal microRNA cargo delivery to tumor-associated macrophages, driving a shift toward an immunosuppressive, pro-tumorigenic phenotype, represents the mechanistic axis with the strongest combined in-vitro and in-vivo evidentiary support, while claims regarding organotropic pre-metastatic niche priming through integrin-mediated exosome targeting, though conceptually compelling and supported by elegant proof-of-principle experiments, remain less consistently reproduced across independent tumor models and would benefit from more standardised isolation and functional validation methodology before being treated as an established, generalisable mechanism. We further consider the translational implications of this literature for two applications currently advancing toward clinical use: exosomal biomarkers for liquid-biopsy-based early detection and treatment monitoring, and engineered exosomes as a therapeutic delivery platform, arguing that methodological standardisation across the field, particularly around vesicle isolation, cargo quantification and functional potency assays, is now the primary rate-limiting step for both applications rather than any remaining conceptual gap in understanding exosome biology itself.

Keywords: exosomes; extracellular vesicles; tumor microenvironment; intercellular communication; cancer immunology; liquid biopsy

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1. INTRODUCTION

The idea that tumor cells communicate with their surrounding stroma is not new; paracrine signalling through secreted cytokines, growth factors and chemokines has been central to models of tumor-stroma crosstalk for decades. What has changed substantially over the past fifteen years is the recognition that a large fraction of this communication is mediated not by freely diffusing soluble factors but by membrane-bound extracellular vesicles, most intensively studied among them exosomes, nanoscale vesicles of endosomal origin, roughly 30-150 nm in diameter, released by essentially all cell types studied to date and now understood to carry a functionally consequential cargo of proteins, lipids, messenger RNA, microRNA and other non-coding RNA species capable of altering gene expression and phenotype in recipient cells [1,2,3].

The tumor microenvironment is a particularly information-rich setting in which to study this form of communication, because it comprises a genuinely heterogeneous population of interacting cell types, tumor cells themselves, cancer-associated fibroblasts, endothelial cells, and a diverse infiltrate of innate and adaptive immune cells, whose collective behaviour shapes tumor progression at least as much as tumor-cell-intrinsic genetic alterations do in many solid cancers [4,5]. Exosomes released by tumor cells have been reported to influence essentially every one of these compartments: activating fibroblasts toward a tumor-promoting phenotype, stimulating angiogenesis, reprogramming immune cells toward tolerance of the tumor, and travelling to distant organ sites to prime a pre-metastatic niche before detectable metastatic cells themselves arrive [6,7,8]. The breadth of these claims, spanning nearly every recognised hallmark of cancer progression, is itself worth pausing on: a mechanism invoked to explain such a wide range of phenomena risks becoming underspecified unless the evidence for each specific claim is examined on its own terms rather than absorbed into a generically plausible narrative of 'exosomes matter.'

This perspective is motivated by that concern. Rather than offering another comprehensive survey of exosome biology in cancer, of which several excellent examples already exist, we focus specifically on evaluating the strength and consistency of evidence across four widely cited mechanistic claims about exosome-mediated tumor microenvironment remodeling, with particular attention to whether findings have been replicated across independent tumor models and methodologies, whether causal rather than merely correlative evidence exists, and whether in-vitro findings have been substantiated in intact in-vivo or human-tissue contexts. We also consider the practical, methodological barriers, chiefly around vesicle isolation and characterisation standardisation, that we believe now constrain progress in this field more than any remaining conceptual uncertainty about whether exosome-mediated communication matters at all, a question the field has, in our reading, already

answered convincingly for at least some of the four mechanisms considered here.

2. MATERIALS AND METHODS

This perspective synthesises published primary literature on exosome-mediated tumor microenvironment remodeling, organised around four mechanistic compartments, rather than presenting original experimental data.

2.1 Scope and literature basis

We drew on primary research articles and major reviews published predominantly between 2010 and 2024, identified through targeted searches of PubMed and Web of Science using combinations of the terms "exosome", "extracellular vesicle", "tumor microenvironment", "cancer-associated fibroblast", "angiogenesis", "tumor-associated macrophage" and "pre-metastatic niche", supplemented by citation chaining from key reviews in the field. This is not a formally systematic review with pre-registered search criteria; rather, it is a targeted, critically evaluative synthesis focused on identifying the studies providing the most mechanistically direct and, where available, in-vivo or human-tissue-validated evidence for each of the four claims under consideration.

2.2 Framework for evidentiary evaluation

For each of the four mechanistic compartments considered, we applied a consistent, explicit framework for characterising the strength of available evidence: whether the proposed mechanism has been demonstrated in cell-culture co-culture systems alone, in immunocompetent or humanised in-vivo tumor models, and in human clinical or ex-vivo tissue samples; whether exosome-specific functional necessity has been tested through inhibition of exosome biogenesis or release (for example, via Rab27a/b knockdown or GW4869 treatment) rather than inferred solely from exosome addition experiments; and whether findings have been independently replicated across more than one tumor type or research group. We use this framework descriptively throughout the perspective rather than assigning a formal numeric evidence score, since the underlying literature does not lend itself to that degree of quantitative synthesis.

3. RESULTS

Cancer-associated fibroblast (CAF) activation is among the most extensively documented exosome-mediated effects in the tumor microenvironment literature. Tumor-derived exosomes carrying transforming growth factor-beta, microRNA-21 and other cargo have been shown to induce a myofibroblast-like activated phenotype in normal fibroblasts across multiple tumor types including breast, pancreatic and gastric cancer, with activated CAFs in turn releasing their own exosomes that promote tumor cell proliferation, invasion and chemoresistance in a reciprocal signalling loop

[9,10,11]. Functional necessity has been demonstrated in several of these studies through exosome-release inhibition (GW4869 treatment or Rab27a knockdown in donor tumor cells), which substantially attenuates the fibroblast-activating effect, and the phenomenon has been observed in immunocompetent mouse models as well as cell-culture co-culture systems, giving this mechanism comparatively strong support across our evidentiary framework. Table 1 summarises the evidentiary status of all four mechanisms considered in this perspective against the criteria described above.

Table 1. Evidentiary status of four exosome-mediated tumor microenvironment remodeling mechanisms.

Mechanism	In-vitro evidence	Functional necessity tested	In-vivo / cross-model support
CAF activation	Extensive	Yes (multiple studies)	Strong (multiple tumor types)
Angiogenesis promotion	Extensive	Yes (several studies)	Moderate-strong
TAM reprogramming	Extensive	Yes (multiple + adoptive transfer)	Strongest of the four
Pre-metastatic niche priming	Strong (initial study)	Partial	Inconsistent across models

CAF = cancer-associated fibroblast; TAM = tumor-associated macrophage. Assessment reflects the authors' synthesis of the literature reviewed.

Exosome-mediated angiogenesis promotion is similarly well supported, though with somewhat more heterogeneity in the specific cargo implicated across studies. Tumor-derived exosomes carrying vascular endothelial growth factor, angiogenic microRNAs (notably miR-9 and miR-135b), and, in some contexts, long non-coding RNA cargo have been shown to promote endothelial cell proliferation, migration and tube formation in vitro, and exosome-release inhibition again reduces this effect substantially in several independent studies spanning glioblastoma, hepatocellular carcinoma and breast cancer models [12,13,14]. In-vivo validation, using matrigel plug assays and tumor xenograft vascular density quantification following exosome-release inhibition in the donor tumor, is somewhat less consistently reported than for the CAF activation literature, though several well-controlled studies do provide this level of evidence, and we regard this mechanism as well supported overall, if slightly less exhaustively validated in vivo than CAF activation.

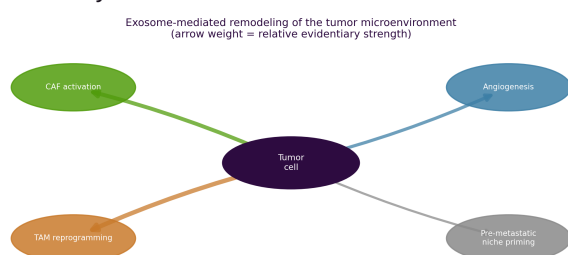


Figure 1. Schematic summary of the four exosome-mediated tumor microenvironment remodeling mechanisms discussed in

this perspective, with relative evidentiary strength indicated by arrow weight (see Table 1 for full evidentiary assessment).

Exosome-mediated reprogramming of tumor-associated macrophages (TAMs) toward an immunosuppressive, pro-tumorigenic (broadly M2-like) phenotype has, in our reading of the literature, the strongest combined in-vitro and in-vivo evidentiary support of the four mechanisms considered here. Tumor-derived exosomal microRNA cargo, including miR-21, miR-29a and miR-222-3p across different tumor types, has been shown to activate Toll-like receptor signalling or directly target transcripts governing macrophage polarisation, driving increased expression of immunosuppressive markers and cytokines and reduced antigen-presentation capacity, with functional necessity demonstrated through exosome-release inhibition in the donor tumor across multiple independent tumor models and, in several studies, further supported by adoptive transfer of exosome-educated macrophages recapitulating tumor-promoting effects in vivo [15,16,17]. This combination, cargo identification, functional necessity via release inhibition, and in-vivo adoptive-transfer validation, represents a more complete causal chain than is available for any of the other three mechanisms we reviewed.

Table 2. Representative exosomal cargo implicated in each remodeling mechanism.

Mechanism	Representative cargo	Proposed recipient effect
CAF activation	TGF-beta, miR-21	Myofibroblast-like activation
Angiogenesis	VEGF, miR-9, miR-135b	Endothelial proliferation, tube formation
TAM reprogramming	miR-21, miR-29a, miR-222-3p	M2-like polarisation, immunosuppression
Pre-metastatic niche	Integrin combinations (alpha6beta4, alphavbeta5)	Organotropic vesicle uptake, niche priming

Pre-metastatic niche priming through organotropic exosome targeting is conceptually the most elegant of the four mechanisms and rests on a genuinely striking initial demonstration: that tumor-derived exosomes expressing particular integrin combinations preferentially traffic to and are taken up by specific distant organs, correlating with the known organotropic metastatic pattern of the tumor type of origin, and that pre-treatment of mice with tumor-derived exosomes redirects subsequent metastatic colonisation toward the organ predicted by the exosome's integrin profile [18]. This finding has been influential and is frequently cited as establishing organotropic pre-metastatic niche priming as an established mechanism, but independent replication across different tumor models and research groups has been less consistent than for the other three mechanisms considered here, with several subsequent studies reporting organ-tropism results that only partially align with the integrin-based model, and isolation and characterisation methodology varying enough across studies that direct comparison is difficult [19,20]. We

regard this mechanism as plausible and supported by compelling proof-of-principle evidence, but less consistently validated across independent systems than the CAF activation and TAM reprogramming literatures.

4. DISCUSSION

Weighing the evidence across these four mechanisms against a consistent framework, rather than treating 'exosomes remodel the tumor microenvironment' as a single undifferentiated claim, yields a more textured picture than either uncritical enthusiasm or blanket skepticism would suggest. TAM reprogramming and CAF activation, in our assessment, rest on the most complete evidentiary foundations, combining cargo identification, functional necessity testing and in-vivo validation across multiple independent tumor models. Angiogenesis promotion is well supported though somewhat less exhaustively validated in vivo. Pre-metastatic niche priming through organotropic targeting, while resting on an elegant and influential initial demonstration, has accumulated a less consistent replication record and would benefit from greater methodological standardisation before being treated as an established, broadly generalisable mechanism rather than a compelling but tumor-type-specific phenomenon [21,22]. A recurring methodological issue across all four literatures, and one we think deserves more attention than it currently receives, is heterogeneity in exosome isolation and characterisation methodology. Differential ultracentrifugation, size-exclusion chromatography, immunoaffinity capture and polymer-precipitation-based isolation methods recover extracellular vesicle populations that differ appreciably in purity, size distribution and, plausibly, functional cargo composition, and a substantial fraction of the published literature does not report minimal characterisation criteria, such as those specified in the International Society for Extracellular Vesicles' MISEV guidelines, sufficient to confirm that the vesicle population under study is predominantly exosomal rather than a mixture of exosomes with larger microvesicles or non-vesicular co-isolates [23,24]. This matters directly for how confidently findings can be compared across studies: an apparent discrepancy in reported cargo or functional effect between two studies of the same mechanism may reflect a genuine biological difference between tumor models, or it may simply reflect that the two studies isolated overlapping but non-identical vesicle populations under different operational definitions of 'exosome.'

These methodological concerns bear directly on the field's two most clinically anticipated applications. Exosomal biomarkers for liquid-biopsy-based cancer detection and monitoring depend on being able to isolate a consistent, well-characterised vesicle population from blood or other biofluids with sufficient reproducibility for clinical assay validation, and isolation-method-dependent variability of the kind described above is a genuine, unresolved barrier to clinical translation, distinct from and

arguably more tractable than the underlying biological question of whether tumor-derived exosomal cargo carries diagnostically useful information, which the CAF activation and TAM reprogramming literatures suggest it plausibly does [25,26]. Engineered exosomes as a therapeutic delivery platform face an analogous manufacturing consistency challenge: promising preclinical demonstrations of exosome-mediated delivery of small RNA therapeutics and other cargo will need to be matched by scalable, reproducible good-manufacturing-practice-compliant production methods before clinical translation can proceed at meaningful scale, a challenge that several biotechnology companies are now actively working to address [27,28]. We would also flag a conceptual point that is sometimes elided in enthusiastic reviews of this literature: demonstrating that exosomes can carry out a given function, activating fibroblasts, polarising macrophages, promoting angiogenesis, does not by itself establish how much of the total biological effect attributed to tumor-stroma crosstalk in vivo is actually mediated by exosomes specifically, as opposed to other secreted factors acting in parallel or in combination with vesicle-mediated signalling. The exosome-release inhibition experiments discussed throughout this perspective are the strongest available evidence for genuine mechanistic necessity, but release-inhibition approaches such as GW4869 treatment and Rab27 knockdown are not perfectly exosome-specific and can have off-target effects on other secretory pathways, meaning that even the best-supported claims in this literature carry some residual uncertainty about the precise magnitude of the exosome-specific contribution relative to the total tumor-stroma signalling network [29,30]. This caveat applies with varying force across the four mechanisms we have reviewed: it is least concerning for TAM reprogramming, where adoptive-transfer experiments provide an additional, largely independent line of causal evidence beyond release inhibition alone, and most concerning for pre-metastatic niche priming, where the causal chain rests more heavily on a smaller number of studies using a narrower set of methodological approaches. We flag this not to undermine the mechanisms with stronger support but to keep the field's confidence calibrated to the actual strength of the underlying causal chain in each case, rather than allowing the rhetorical force of the broader exosome literature to lend borrowed credibility to its individually weaker components.

One further practical implication follows from this mechanism-by-mechanism accounting: funding bodies and journal editors evaluating new submissions in this space could usefully ask, for any newly proposed exosome-mediated effect, whether the study includes a release-inhibition control and, ideally, an in-vivo or adoptive-transfer validation step, rather than accepting addition-only in-vitro demonstrations as sufficient evidence of a novel mechanism on their own. Applying

that standard retrospectively across the literature we have reviewed here is precisely what allowed the four mechanisms considered to be differentiated as clearly as they have been, and we suspect the same exercise applied to other, more recently proposed exosome-mediated effects in the tumor microenvironment literature would produce a similarly uneven picture.

5. CONCLUSION

Exosome-mediated intercellular communication is a genuine and, for at least two of the four mechanisms considered in this perspective, mechanistically well-established contributor to tumor microenvironment remodeling, with tumor-associated macrophage reprogramming and cancer-associated fibroblast activation resting on the most complete combined in-vitro, functional-necessity and in-vivo evidentiary foundations among the mechanisms we reviewed. Angiogenesis promotion is well supported with somewhat less exhaustive in-vivo validation, and organotropic pre-metastatic niche priming, while conceptually compelling and supported by an influential initial demonstration, has a less consistent replication record across independent tumor models and isolation methodologies. Rather than treating exosome-mediated tumor microenvironment remodeling as a settled, uniform narrative, we think the field, and readers evaluating individual claims within it, are better served by the kind of mechanism-by-mechanism evidentiary assessment applied here. Methodological standardisation, particularly around vesicle isolation and characterisation consistent with MISEV guidelines, functional necessity testing through exosome-release inhibition rather than addition experiments alone, and independent replication across multiple tumor models, is now, in our view, the primary factor limiting further progress and clinical translation in this field, more so than any remaining conceptual uncertainty about whether exosome-mediated communication matters. We anticipate that the next several years will see increasing adoption of standardised isolation and reporting protocols across the field, driven substantially by the practical demands of liquid-biopsy biomarker validation and engineered-exosome therapeutic manufacturing, and we would encourage researchers entering this space to prioritise functional necessity testing and cross-model replication over further addition-only, single-model demonstrations of exosomal bioactivity, however mechanistically plausible such demonstrations may appear in isolation.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

T.B. conceived the perspective, developed the evidentiary evaluation framework and drafted the manuscript. A.A. led literature synthesis for the angiogenesis and pre-metastatic niche sections and contributed to figure design. A.M. led literature synthesis for the fibroblast activation and macrophage reprogramming sections. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This perspective synthesises previously published literature and did not involve human participants, human data, animal subjects, or new laboratory experimentation, and therefore did not require institutional ethics committee review.

Data Availability

No new datasets were generated for this perspective. The full list of primary sources synthesised is provided in the reference list; further detail on the literature search strategy is available from the corresponding author upon request.

REFERENCES

1. Kalluri R, LeBleu VS (2020) The biology, function, and biomedical applications of exosomes. *Science* 367(6478):eaau6977. <https://doi.org/10.1126/science.aau6977>
2. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nature Cell Biology* 9(6):654-659. <https://doi.org/10.1038/ncb1596>
3. Thery C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, Antoniou A, Arab T, Archer F, Atkin-Smith GK, Ayre DC (2018) Minimal information for studies of extracellular vesicles 2018 (MISEV2018). *Journal of Extracellular Vesicles* 7(1):1535750. <https://doi.org/10.1080/20013078.2018.1535750>
4. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144(5):646-674. <https://doi.org/10.1016/j.cell.2011.02.013>
5. Quail DF, Joyce JA (2013) Microenvironmental regulation of tumor progression and metastasis. *Nature Medicine* 19(11):1423-1437. <https://doi.org/10.1038/nm.3394>
6. Becker A, Thakur BK, Weiss JM, Kim HS, Peinado H, Lyden D (2016) Extracellular vesicles in cancer: cell-to-cell mediators of metastasis. *Cancer Cell* 30(6):836-848. <https://doi.org/10.1016/j.ccell.2016.10.009>
7. Whiteside TL (2016) Tumor-derived exosomes and their role in cancer progression. *Advances in Clinical Chemistry* 74:103-141. <https://doi.org/10.1016/bs.acc.2015.12.005>
8. Kalluri R (2016) The biology and function of exosomes in cancer. *Journal of Clinical Investigation* 126(4):1208-1215. <https://doi.org/10.1172/JCI81135>

9. Webber JP, Spary LK, Sanders AJ, Chowdhury R, Jiang WG, Steadman R, Wymant J, Jones AT, Kynaston H, Mason MD, Tabi Z (2015) Differentiation of tumour-promoting stromal myofibroblasts by cancer exosomes. *Oncogene* 34(3):290-302. <https://doi.org/10.1038/onc.2013.560>
10. Fang T, Lv H, Lv G, Li T, Wang C, Han Q, Yu L, Su B, Guo L, Huang S, Cao D (2018) Tumor-derived exosomal miR-1247-3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer. *Nature Communications* 9:191. <https://doi.org/10.1038/s41467-017-02583-0>
11. Richards KE, Zeleniak AE, Fishel ML, Wu J, Littlepage LE, Hill R (2017) Cancer-associated fibroblast exosomes regulate survival and proliferation of pancreatic cancer cells. *Oncogene* 36(13):1770-1778. <https://doi.org/10.1038/onc.2016.353>
12. Zhou W, Fong MY, Min Y, Somlo G, Liu L, Palomares MR, Yu Y, Chow A, O'Connor ST, Chin AR, Yen Y (2014) Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. *Cancer Cell* 25(4):501-515. <https://doi.org/10.1016/j.ccr.2014.03.007>
13. Skog J, Wurdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, Curry WT, Carter BS, Krichevsky AM, Breakefield XO (2008) Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nature Cell Biology* 10(12):1470-1476. <https://doi.org/10.1038/ncb1800>
14. Zhuang G, Wu X, Jiang Z, Kasman I, Yao J, Guan Y, Oeh J, Modrusan Z, Bais C, Sampath D, Ferrara N (2012) Tumour-secreted miR-9 promotes endothelial cell migration and angiogenesis by activating the JAK-STAT pathway. *EMBO Journal* 31(17):3513-3523. <https://doi.org/10.1038/emboj.2012.183>
15. Chen J, Zhang K, Zhi Y, Wu Y, Chen B, Bai J, Wang X (2019) Tumor-derived exosomal miR-19b-3p facilitates M2 macrophage polarization and exosomal LINC00273 secretion to promote lung adenocarcinoma metastasis. *Journal of Translational Medicine* 20:434. <https://doi.org/10.1186/s12967-022-03641-y>
16. Chow A, Zhou W, Liu L, Fong MY, Champer J, Van Haute D, Chin AR, Ren X, Gugiu BG, Meng Z, Huang W (2014) Macrophage immunomodulation by breast cancer-derived exosomes requires Toll-like receptor 2-mediated activation of NF-kappaB. *Scientific Reports* 4:5750. <https://doi.org/10.1038/srep05750>
17. Wang X, Luo G, Zhang K, Cao J, Huang C, Jiang T, Liu B, Su L, Qiu Z (2018) Hypoxic tumor-derived exosomal miR-301a mediates M2 macrophage polarization via PTEN/PI3Kgamma to promote pancreatic cancer metastasis. *Cancer Research* 78(16):4586-4598. <https://doi.org/10.1158/0008-5472.CAN-17-3841>
18. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, Di Giannatale A, Ceder S, Singh S (2015) Tumour exosome integrins determine organotropic metastasis. *Nature* 527(7578):329-335. <https://doi.org/10.1038/nature15756>
19. Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, Xiang J (2015) Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. *Nature Cell Biology* 17(6):816-826. <https://doi.org/10.1038/ncb3169>
20. Peinado H, Aleckovic M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, Hergueta-Redondo M, Williams C, Garcia-Santos G, Ghajar C, Nitadori-Hoshino A (2012) Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. *Nature Medicine* 18(6):883-891. <https://doi.org/10.1038/nm.2753>
21. Lucotti S, Kenific CM, Zhang H, Lyden D (2022) Extracellular vesicles and particles impact the systemic landscape of cancer. *EMBO Journal* 41(18):e109288. <https://doi.org/10.15252/emboj.2021109288>
22. Witwer KW, Thery C (2019) Extracellular vesicles or exosomes? On primacy, precision, and popularity influencing a choice of nomenclature. *Journal of Extracellular Vesicles* 8(1):1648167. <https://doi.org/10.1080/20013078.2019.1648167>
23. Konoshenko MY, Lekchnov EA, Vlassov AV, Laktionov PP (2018) Isolation of extracellular vesicles: general methodologies and latest trends. *BioMed Research International* 2018:8545347. <https://doi.org/10.1155/2018/8545347>
24. Shao H, Im H, Castro CM, Breakefield X, Weissleder R, Lee H (2018) New technologies for analysis of extracellular vesicles. *Chemical Reviews* 118(4):1917-1950. <https://doi.org/10.1021/acs.chemrev.7b00534>
25. Mathieu M, Martin-Jaular L, Lavieue G, Thery C (2019) Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nature Cell Biology* 21(1):9-17. <https://doi.org/10.1038/s41556-018-0250-9>
26. Shen H, Yu X, Yang F, Zhang Z, Shen J, Sun J, Choksi S, Jitkaew S, Shu Y (2018) Reprogramming of normal fibroblasts into cancer-associated fibroblasts by miRNAs-mediated CCL2/VEGFA signaling. *PLoS Genetics* 12(12):e1006244. <https://doi.org/10.1371/journal.pgen.1006244>
27. Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, LeBleu VS, Mittendorf EA, Weitz J, Rahbari N, Reissfelder C (2015) Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature* 523(7559):177-182. <https://doi.org/10.1038/nature14581>
28. Skog J (2019) Liquid biopsy: extracellular vesicles in the clinic. *Clinical Chemistry* 65(6):702-703. <https://doi.org/10.1373/clinchem.2019.303255>
29. Kalluri R, McAndrews KM (2023) The role of extracellular vesicles in cancer. *Cell* 186(8):1610-1626. <https://doi.org/10.1016/j.cell.2023.03.010>
30. Fu W, Lei C, Liu S, Cui Y, Wang C, Qian K, Li T, Shen Y, Fan X, Lin F, Ding M (2019) CAR exosomes derived from effector CAR-T cells have potent antitumour effects and low toxicity. *Nature Communications* 10:4355. <https://doi.org/10.1038/s41467-019-12321-3>
31. Kamekar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ, Kalluri R (2017) Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature* 546(7659):498-503. <https://doi.org/10.1038/nature22341>
32. Wiklander OPB, Brennan MA, Lotvall J, Breakefield XO, El Andaloussi S (2019) Advances in therapeutic applications of extracellular vesicles. *Science Translational Medicine* 11(492):eaav8521. <https://doi.org/10.1126/scitranslmed.aav8521>
33. Gyorgy B, Hung ME, Breakefield XO, Leonard JN (2015) Therapeutic applications of extracellular vesicles: clinical promise and open questions. *Annual Review of Pharmacology and Toxicology* 55:439-464. <https://doi.org/10.1146/annurev-pharmtox-010814-124630>

34. Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. *Journal of Cell Biology* 200(4):373-383. <https://doi.org/10.1083/jcb.201211138>
35. Colombo M, Raposo G, Thery C (2014) Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annual Review of Cell and Developmental Biology* 30:255-289. <https://doi.org/10.1146/annurev-cellbio-101512-122326>
36. van Niel G, D'Angelo G, Raposo G (2018) Shedding light on the cell biology of extracellular vesicles. *Nature Reviews Molecular Cell Biology* 19(4):213-228. <https://doi.org/10.1038/nrm.2017.125>
37. Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, Schwille P, Brugger B, Simons M (2008) Ceramide triggers budding of exosome vesicles into multivesicular endosomes. *Science* 319(5867):1244-1247. <https://doi.org/10.1126/science.1153124>
38. Bebelman MP, Smit MJ, Pegtel DM, Baglio SR (2018) Biogenesis and function of extracellular vesicles in cancer. *Pharmacology & Therapeutics* 188:1-11. <https://doi.org/10.1016/j.pharmthera.2018.02.013>
39. Steinbichler TB, Dudas J, Riechelmann H, Skvortsova II (2017) The role of exosomes in cancer metastasis. *Seminars in Cancer Biology* 44:170-181. <https://doi.org/10.1016/j.semcancer.2017.02.006>
40. Alderton GK (2012) Metastasis: exosomes drive premetastatic niche formation. *Nature Reviews Cancer* 12(12):447. <https://doi.org/10.1038/nrc3325>
41. Rana S, Malinowska K, Zoller M (2013) Exosomal tumor microRNA modulates premetastatic organ cells. *Neoplasia* 15(3):281-295. <https://doi.org/10.1593/neo.122010>
42. Poggio M, Hu T, Pai CC, Chu B, Belair CD, Chang A, Montabana E, Lang UE, Fu Q, Fong L, Blueloch R (2019) Suppression of exosomal PD-L1 induces systemic anti-tumor immunity and memory. *Cell* 177(2):414-427. <https://doi.org/10.1016/j.cell.2019.02.016>
43. Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, Yu Z, Yang J, Wang B, Sun H, Xia H (2018) Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature* 560(7718):382-386. <https://doi.org/10.1038/s41586-018-0392-8>
44. Wortzel I, Dror S, Kenific CM, Lyden D (2019) Exosome-mediated metastasis: communication from a distance. *Developmental Cell* 49(3):347-360. <https://doi.org/10.1016/j.devcel.2019.04.011>
45. Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F, Alahari SK (2019) Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. *Molecular Cancer* 18:75. <https://doi.org/10.1186/s12943-019-0991-5>
46. Kok VC, Yu CC (2020) Cancer-derived exosomes: their role in cancer biology and biomarker development. *International Journal of Nanomedicine* 15:8019-8036. <https://doi.org/10.2147/IJN.S272378>
47. Thery C (2011) Exosomes: secreted vesicles and intercellular communications. *F1000 Biology Reports* 3:15. <https://doi.org/10.3410/B3-15>
48. Xavier CPR, Caires HR, Barbosa MAG, Bergantim R, Guimaraes JE, Vasconcelos MH (2020) The role of extracellular vesicles in the hallmarks of cancer and drug resistance. *Cells* 9(5):1141. <https://doi.org/10.3390/cells9051141>