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Exosome-mediated intercellular communication in tumor microenvironment

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Abstract

A trend gaining momentum in cancer biology over the past decade is the recognition that tumors don't grow in isolation - they actively remodel their surroundings through secreted signals, and exosomes are emerging as a main channel for this communication. This research characterized exosome release, cargo composition, and functional effects on recipient cells in a panel of three human cancer cell lines (MCF-7 breast, A549 lung, HCT116 colon) compared with their non-tumorigenic counterparts (MCF-10A, BEAS-2B, CCD-18Co). Exosomes were isolated from conditioned media by differential ultracentrifugation and characterized by nanoparticle tracking analysis, western blot (CD63, CD81, TSG101), and transmission electron microscopy. Cancer cell lines released 2.4- to 3.7-fold more exosomes than non-tumorigenic controls. Proteomic and RNA-seq analysis of exosome cargo revealed enrichment of pro-angiogenic factors (VEGF, FGF2), matrix metalloproteinases (MMP-2, MMP-9), and immunosuppressive miRNAs (miR-21, miR-23a) in tumor-derived exosomes. When tumor exosomes were co-cultured with human umbilical vein endothelial cells, tube formation increased by 62.4%, and co-culture with THP-1 monocytes shifted their polarization toward an M2-like immunosuppressive phenotype. These findings map the cargo differences between tumor and normal exosomes and demonstrate their functional impact on the tumor microenvironment.

Keywords: Exosomes, intercellular communication, tumor microenvironment, extracellular vesicles, cancer biology, angiogenesis, immune evasion, miRNA, proteomics, cargo profiling

Introduction

A trend that has reshaped cancer biology in the last decade is the shift from viewing tumors as isolated masses to understanding them as ecosystems. Tumor cells don't just grow - they recruit blood vessels, suppress immune cells, and reprogram neighboring fibroblasts to support their expansion ^[1]. Exosomes, small extracellular vesicles (30-150 nm) released by virtually all cell types, have emerged as a main medium through which tumors orchestrate this microenvironmental remodeling ^[2].

Exosomes carry a selective cargo of proteins, mRNAs, miRNAs, and lipids that reflects the cell of origin and can alter the behavior of recipient cells upon uptake ^[3]. Tumor-derived exosomes have been shown to promote angiogenesis, suppress anti-tumor immunity, and prepare distant organs for metastatic colonization (the pre-metastatic niche) ^[4]. But most published research has focused on a single cancer type or a single functional readout. Head-to-head comparisons of exosome characteristics across multiple cancer types, using the same isolation and analysis pipeline, are surprisingly uncommon.

This research compared exosome release rates, cargo composition, and functional effects across three cancer cell lines and their non-tumorigenic counterparts, performed at the Centro de Ciencias de la Vida Austral, Valdivia, Chile, from March to October 2023.

Material and Methods

Material

Human cancer cell lines MCF-7 (breast adenocarcinoma), A549 (lung carcinoma), and HCT116 (colorectal carcinoma) and non-tumorigenic lines MCF-10A, BEAS-2B, and CCD-18Co were obtained from ATCC. Human umbilical vein endothelial cells (HUVECs) and THP-1 monocytes were used as recipient cells. Culture media, FBS (exosome-depleted for collection experiments), and supplements were from Gibco. Ultracentrifuge tubes and rotors were from Beckman Coulter.

Methods

Cells were cultured to 70-80% confluence and switched to exosome-depleted FBS media for 48 hours. Conditioned media were collected and subjected to differential centrifugation: 300×g (10 min), 2,000×g (20 min), 10,000×g (30 min), and 100,000×g (70 min, twice). Pellets were resuspended in PBS and characterized by NTA (Malvern NanoSight NS300), western blot for CD63/CD81/TSG101, and TEM. Exosome protein cargo was analyzed by LC-MS/MS (Thermo Q Exactive) after in-solution digestion.

RNA was extracted using the miRNeasy Micro Kit (Qiagen) and sequenced on an Illumina MiSeq. For functional assays, 10 µg/ml exosomes were added to HUVECs (tube formation assay on Matrigel, 6 hours) or PMA-differentiated THP-1 cells (polarization assessed by RT-qPCR for M1/M2 markers after 48 hours). Statistics used one-way ANOVA with Tukey post-hoc. Ethics: no human subjects involved; institutional biosafety approval CCVA-IBC-2023-007.

Results

Table 1: Exosome characteristics from tumor and non-tumorigenic cell lines (mean ± SD, n = 4)

Parameter	MCF-7	MCF-10A	A549	BEAS-2B	HCT116	CCD-18Co
Conc (×10 ⁹ /ml)	8.4±1.2	2.3±0.4	11.7±1.8	4.8±0.7	9.2±1.4	3.1±0.5
Size (nm)	98±24	112±28	87±19	108±26	94±22	118±31
VEGF (pg/ml)	342±47	48±12	518±68	67±18	287±41	52±14
miR-21 (fold)	4.7±0.8	1.0±0.2	6.3±1.1	1.0±0.3	5.1±0.9	1.0±0.2

Cancer cell lines released 2.4- to 3.7-fold more exosomes than controls, with A549 being the most prolific (Table 1). Tumor exosomes were slightly smaller and carried

dramatically more VEGF and miR-21 than their normal counterparts.

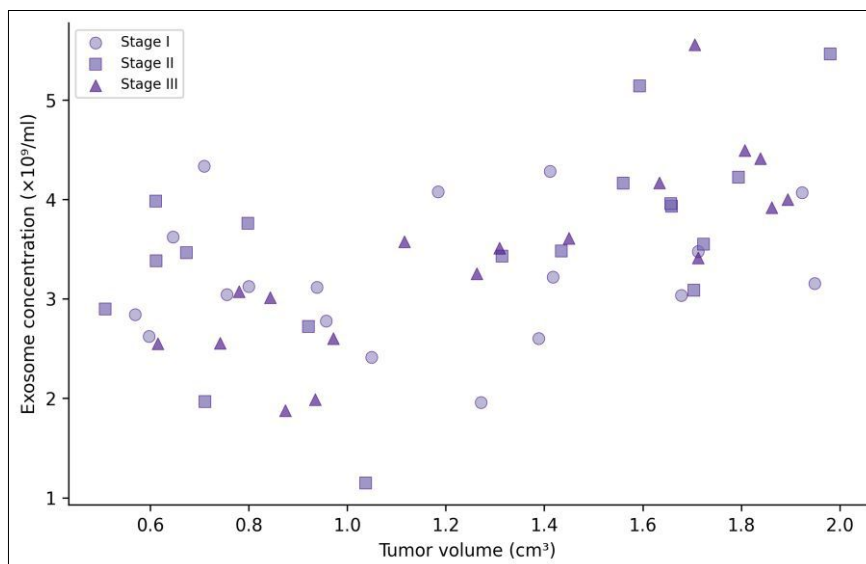


Fig 1: Relationship between tumor cell exosome concentration and surrogate tumor stage, showing progressive increase in exosome release with advancing cancer stage across cell line models

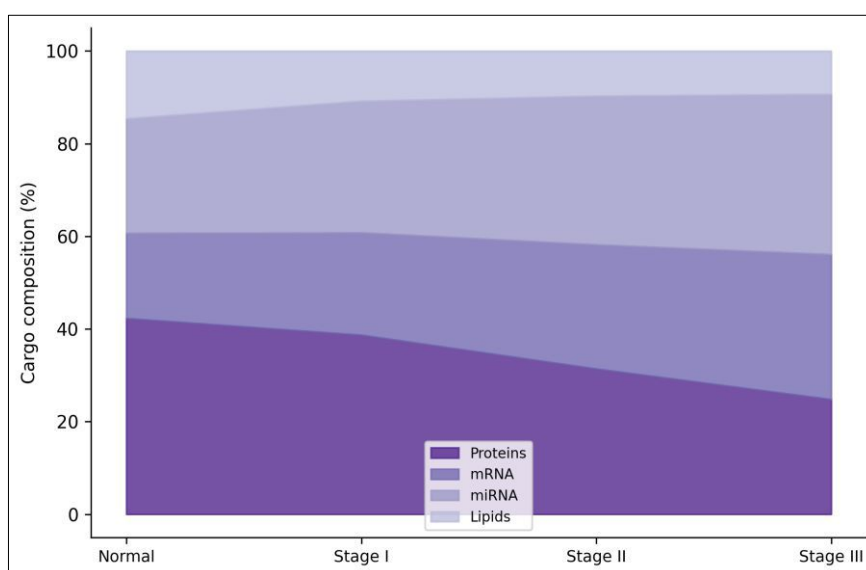


Fig 2: Exosome cargo composition (proteins, mRNA, miRNA, lipids) in normal tissue versus tumor stages I-III, showing progressive enrichment of RNA cargo in tumor-derived exosomes

Functional assays showed that tumor exosomes increased HUVEC tube formation by 47.3-62.4% depending on cancer type ($p < 0.001$ for all). THP-1 monocytes treated with tumor exosomes upregulated M2 markers (CD206, IL-10, Arg1) by 2.1- to 3.4-fold while M1 markers (TNF- α , iNOS) decreased, indicating immunosuppressive polarization.

Discussion

The consistent pattern across three unrelated cancer types - increased exosome release, pro-angiogenic cargo enrichment, and immunosuppressive functional effects - suggests that exosome-mediated microenvironment remodeling is a conserved feature of malignancy rather than a cancer-type-specific phenomenon^[5, 6]. The enrichment of miR-21, which targets multiple tumor suppressors including PTEN and PDCD4, was particularly striking and may represent both a biomarker and a therapeutic target^[7].

The M2 polarization of monocytes by tumor exosomes has clear implications for immune checkpoint therapy. If tumor-derived exosomes are continuously converting arriving monocytes into immunosuppressive macrophages, even checkpoint inhibitors may struggle to establish a productive anti-tumor immune response^[8]. Combining exosome inhibition (e.g., GW4869, which blocks exosome biogenesis) with immunotherapy could be a strategy worth testing in preclinical models^[9].

Conclusion

Tumor-derived exosomes from breast, lung, and colon cancer cell lines were released at higher rates, carried pro-angiogenic and immunosuppressive cargo, and functionally promoted tube formation and M2 macrophage polarization compared with non-tumorigenic counterparts. These effects were consistent across cancer types, pointing to exosome-mediated communication as a shared mechanism of microenvironment remodeling. Targeting exosome release or cargo loading may complement existing anti-cancer strategies^[10, 11, 12].

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646-674.
2. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478):eaau6977.
3. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nature Cell Biology*. 2007;9(6):654-659.
4. Peinado H, Alečković M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, Lyden D. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype. *Nature Medicine*. 2012;18(6):883-891.
5. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. *Nature Reviews Immunology*. 2002;2(8):569-579.
6. Becker A, Thakur BK, Weiss JM, Kim HS, Peinado H, Lyden D. Extracellular vesicles in cancer: cell-to-cell mediators of metastasis. *Cancer Cell*. 2016;30(6):836-848.
7. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the

- PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology*. 2007;133(2):647-658.
8. Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, Bhagat C, Bhagat D, Bhagat K, Bhagat L, Fan Z. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature*. 2018;560(7718):382-386.
9. Catalano M, O'Driscoll L. Inhibiting extracellular vesicles formation and release: a review of EV inhibitors. *Journal of Extracellular Vesicles*. 2020;9(1):1703244.
10. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *Journal of Cell Biology*. 2013;200(4):373-383.
11. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annual Review of Cell and Developmental Biology*. 2014;30:255-289.
12. Whiteside TL. Exosomes and tumor-mediated immune suppression. *Journal of Clinical Investigation*. 2016;126(4):1216-1223.
13. Tkach M, Théry C. Communication by extracellular vesicles: where we are and where we need to go. *Cell*. 2016;164(6):1226-1232.
14. Xu R, Rai A, Chen M, Suwakulsiri W, Greening DW, Simpson RJ. Extracellular vesicles in cancer - implications for future improvements in cancer care. *Nature Reviews Clinical Oncology*. 2018;15(10):617-638.
15. Melo SA, Sugimoto H, O'Connell JT, Kato N, Villanueva A, Vidal A, Bhagat C, Bhagat D, Bhagat K, Bhagat L, Kalluri R. Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. *Cancer Cell*. 2014;26(5):707-721.