



## PATHOGENETIC SIGNIFICANCE OF CIRCULATING BIOMARKERS: THE ROLE OF MICROVESICLES

L. Catani

Istituto di Ematologia "L. e A. Seràgnoli", Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

Circulating biomarkers are gaining increasing relevance for understanding pathogenetic mechanisms, as well as for the diagnosis and monitoring of hematological malignancies. Among these, extracellular vesicles (EVs), including small and large EVs, are emerging as key mediators of intercellular communication and modulators of the tumor microenvironment. EVs are membrane-bound structures ranging from approximately 100 to 3,000-5,000 nm, containing proteins, lipids, and nucleic acids that reflect the biological and functional state of their cell of origin. In hematological cancers such as acute and chronic leukemias, lymphomas, and multiple myeloma, EVs are released by both neoplastic cells and stromal or immune cells within the microenvironment. Experimental evidence indicates that EVs actively contribute to disease progression by promoting tumor cell survival, angiogenesis, immune evasion, and resistance to therapy. EV-mediated transfer of oncoproteins, microRNAs, and pro-survival signals can reprogram recipient cells, fostering the formation of a microenvironment permissive to clonal expansion. Moreover, EVs contribute to the procoagulant and inflammatory state characteristic of many hematological malignancies. EVs expressing tissue factor or phosphatidylserine promote hypercoagulability, which is associated with thrombotic complications and poorer prognosis. Tumor-derived EVs may also impair antitumor immunity by inhibiting T-cell and NK-cell function or by promoting the expansion of immunosuppressive cell populations.

From a translational point of view, EVs are redefining the concept of liquid biopsy. The analysis of circulating EVs offers a promising, non-invasive approach for disease characterization. EV abundance, cellular origin, and molecular cargo may provide clinically relevant information for diagnosis, prognosis, and therapeutic monitoring, including responses to targeted therapies and immunotherapies. These advances may enable novel prognostic stratification models and therapeutic strategies aimed at disrupting EV-mediated communication. However, clinical implementation requires further

standardization of EV isolation and characterization methods, as well as validation in large prospective studies.

In conclusion, EVs represent both highly informative circulating biomarkers and active pathogenetic mediators in hematological malignancies. Deciphering their biological functions may unlock new diagnostic and therapeutic opportunities, offering innovative targets for the future of experimental hematology.

### References

1. **Welsh JA et al.** — *Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches.* J Extracell Vesicles (2024) 13:e12404. <https://doi.org/10.1002/jev2.12404>
2. **Caivano A et al.** — *High serum levels of extracellular vesicles expressing malignancy-related markers are released in patients with various types of hematological neoplastic disorders.* Tumour Biol (2015) 36:9739–9752. <https://doi.org/10.1007/s13277-015-3741-3>
3. **Hefley BS et al.** — *Characterizing Extracellular Vesicles from Biological Fluids.* J Vis Exp. 2025 Feb 28;(216). doi: 10.3791/67699.
4. **Crescitelli R et al.** — *Subpopulations of extracellular vesicles from human metastatic melanoma tissue identified by quantitative proteomics after optimized isolation.* Nat Protoc (2021) 16:1548–1580. DOI: <https://doi.org/10.1038/s41596-020-00446-1>
5. **Catani L et al.** — *The Power of Extracellular Vesicles in Myeloproliferative Neoplasms: "Crafting" a Microenvironment That Matters.* Cells (2021) 10(9):2316. <https://doi.org/10.3390/cells10092316>
6. **Forte D et al.** — *Nat Commun (2024) 15:10878.* DOI: <https://doi.org/10.1038/s41467-024-55178-1>
7. **Das K et al.** — *Biomolecules (2023) 13(6):897.* DOI: <https://doi.org/10.3390/biom13060897>