

**Research Article****SINGLE-CELL MECHANICS OF CANCER METASTASIS: A MECHANICAL CASCADE PERSPECTIVE****Anastasiia Korolenko and *Tamás Kovács**

A&J School, London, 200 Upper Richmond Road, United Kingdom

Received 14th August 2026; **Accepted** 18th September 2026; **Published online** 16th October 2026

Abstract

Cancer metastasis remains the predominant driver of malignancy-related mortality, accounting for approximately 15% of annual deaths globally. While traditional oncological research focuses heavily on genetic and biochemical signaling networks, metastasis is fundamentally a physical process. To establish secondary lesions, tumor cells must leave the primary tumor mass, survive transport through the circulatory or lymphatic networks, adhere to distant vascular walls, and extravasate into target organs. Each stage of this metastatic cascade acts as a stringent mechanical filter, exerting severe physical selection pressures, such as fluid shear stress, compressive forces, and steric microenvironmental confinement, that eliminate vulnerable tumor cells. This review provides a comprehensive synthesis of single-cell and cell-cluster mechanics across the four critical stages of the hematogenous metastatic cascade: intravasation, circulation, arrest/adhesion, and extravasation. We detail how structural determinants, including nuclear lamina composition, LINC-mediated nucleoskeletal-cytoskeletal coupling, and integrin-mediated mechanotransduction, allow adaptive tumor cells to overcome physical barriers. Furthermore, we evaluate the biomechanical advantages of multicellular circulating tumor cell (CTC) clusters, exploring how heterotypic associations and extracellular matrix scaffolding enhance mechanical survival. By integrating quantitative parameters, such as permissive hemodynamic flow velocities (400–600 m/s) and receptor-ligand stabilization forces (80–200 pN), with molecular pathways (VEGFR2, YAP, TRPV4, and VE-cadherin), this review highlights mechanobiology as a crucial framework for predicting prognosis and identifying novel mechanotherapeutic vulnerabilities in advanced metastatic disease.

Keywords: Mechanobiology, Metastatic Cascade, Circulating Tumor Cells (CTCs), Nuclear Deformability, Mechanotransduction, Hemodynamics.

INTRODUCTION

Cancer metastasis remains one of the leading factors in cancer-related mortality, while cancer itself remains one of the major drivers of all-cause mortality worldwide. Approximately 15% of annual global deaths are directly attributable to malignant neoplasms. During the metastatic cascade, tumor cells leave the primary tumor mass and spread through the body via the circulatory or lymphatic systems, colonizing distant organs and forming secondary tumors. Once cancer becomes established across multiple organs, treatment becomes exceedingly difficult, and patient prognoses deteriorate markedly. Unlike localized primary tumors, which can frequently be managed with surgical resection or targeted local radiotherapy, metastatic cancer presents a much more diffuse, systemic, and heterogeneous challenge that is not vulnerable to localized therapeutic approaches. Unraveling the mechanisms governing metastatic spread is therefore of paramount clinical importance. Metastasis is inherently a mechanical process. Throughout their migratory journey, tumor cells must constantly interact with and deform within highly complex, restrictive, and dynamic mechanical environments. Many of these physical forces are damaging or lethal to cells: fluid shear stress eliminates a vast fraction of circulating tumor cells; physical confinement during migration can cause catastrophic nuclear rupture or severe DNA damage; and high compressive stress during intravasation or extravasation can induce mechanical apoptosis. Consequently, these mechanical forces constitute stringent physical filters or evolutionary selection pressures that shape the survival landscape of cancer within the body. They systematically eliminate fragile, maladaptive cells while enriching subpopulations possessing

high mechanical integrity, superior deformability, and adaptive force-sensing capabilities. Mechanobiology thus directly links physical forces to the evolutionary dynamics of metastatic progression.

Intravasation: Mechanical filters of the primary microenvironment**Tumour microenvironment stiffness and stromal remodelling**

As a primary tumor expands within a confined anatomical space, compressive stresses rapidly escalate within the tumor core, the surrounding extracellular matrix (ECM), and the adjacent stroma. Initially, the host microenvironment produces substantial mechanical resistance to tumor growth. However, persistent tumor growth and metabolic demands drive extensive stromal remodeling through a combination of reciprocal mechanical pressure and biochemical signaling cascades. This remodeling radically transforms the architectural structure and physical mechanics of the local ECM. Activated cancer-associated fibroblasts (CAFs) exert high traction forces, pulling, bundling, and organizing local type-I collagen fibers. Concurrently, lysyl oxidase (LOX) enzymes upregulated by hypoxic tumor cells catalyze dense collagen crosslinking (Dattani *et al.*, 2024). Figure 1 below shows the biomedical cascade in the initial phase.

This matrix reorganization leads to pronounced ECM stiffening, macroscopic collagen alignment, and subsequent integrin clustering on the tumor cell surface, which collectively support directional tumor cell invasion toward peripheral blood vessels. Crucially, elevated ECM stiffness acts as a major mechanical morphogen, promoting epithelial cells to undergo the Epithelial-Mesenchymal Transition (EMT).

*Corresponding Author: **Tamás Kovács**,
A&J School, London, 200 Upper Richmond Road, United Kingdom.

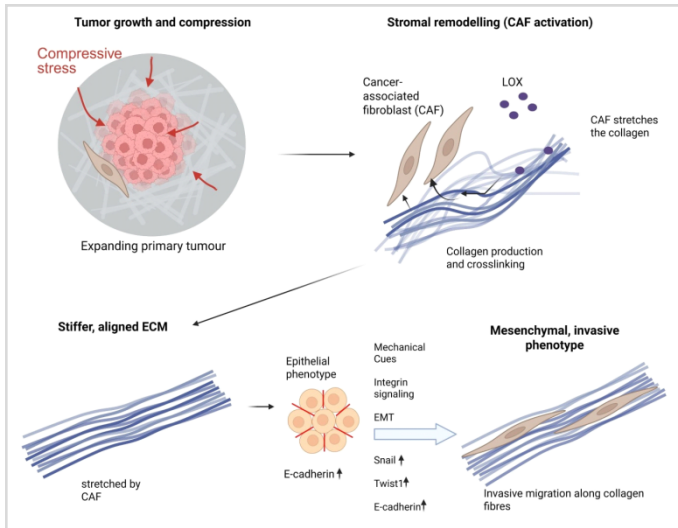


Figure 1. Biomechanical cascade induction of the invasive state. Progression tracking map showing how initial microenvironmental physical growth parameters trigger genetic transitions and structural alterations

During EMT, epithelial cancer cells shed their apical-basal polarity and downregulate intercellular adhesion proteins such as E-cadherin, helping individual cancer cells detach and adapt autonomously. Concurrently, they acquire an elongated, spindle-like mesenchymal morphology that is structurally optimized for forward migration. This structural metamorphosis is driven by intensive cytoskeletal remodeling, which allows cells to become highly invasive and motile. These biophysical modifications are vital within a stiffened microenvironment, as tumor cells must continuously deform and modulate their internal viscoelastic properties to squeeze through dense, remodeled stromal gaps. Therefore, EMT represents a functional cellular adaptation to the mechanical challenges imposed by stromal remodeling; it does not eliminate the physical barrier, but drastically increases the cell's capability to move through the matrix and successfully intravasate. This invasive program is strictly governed by core EMT transcription factors, including Snail and Twist1. Experimental deactivation of either Snail or Twist1 halts this mechanical adaptation, resulting in a profound decrease in cell migration velocity and a complete failure to invade dense matrices.

Cell and nuclear deformability

When tumor cells encounter a stiffened, highly confined ECM, their physical capacity to invade depends heavily on their cell-intrinsic mechanical properties. During intravasation, cells must undergo massive structural deformation to navigate the narrow interstitial pores of the ECM, penetrate the dense, crosslinked basement membrane, and slip between endothelial cell-cell junctions. Overly rigid tumor cells stall and fail to clear these physical barriers, whereas highly compliant, deformable cells readily migrate through the matrix to access the boundary of the bloodstream. Biophysical analyses reveal that the cell nucleus is the ultimate rate-limiting obstacle during migration through confined three-dimensional environments. The nucleus is typically the largest, densest, and stiffest organelle within the eukaryotic cell, possessing an elastic modulus up to ten times greater than that of the surrounding cytoplasm. Nuclear stiffness and mechanical resistance to deformation are predominantly regulated by the

nuclear lamina, a dense, mesh-like structural network lining the inner nuclear membrane, composed of A-type lamins (lamins A and C) and B-type lamins. A compliant, soft nucleus containing low ratios of lamin A to lamin C allows highly metastatic cancer cells to squeeze through microscopic endothelial pores and dense matrix constrictions that would otherwise block normal cells. However, this mechanical compliance presents a severe biological trade-off: a soft, hypomorphic nucleus risks excessive structural distortion under migration-induced stress. This extreme deformation can induce localized nuclear envelope rupture, transient herniation of chromatin into the cytoplasm, and catastrophic DNA double-strand breaks due to exposure to cytoplasmic nucleases. This cycle of rupture and repair drives extensive genomic instability and promotes clonal evolution. Successful intravasation thus dictates a strict homeostatic balance between structural deformability and mechanical functionality, ensuring the cell can pass through tight vascular junctions without incurring lethal genomic damage.

Circulation: Physical pressures and cluster dynamics in the bloodstream

Fluid shear stress and hemodynamic survival

Upon crossing the endothelial barrier and entering the bloodstream, circulating tumor cells (CTCs) experience a profound change in their mechanical environment. They are immediately stripped of their stable extracellular matrix attachments and subjected to fluid shear stress (FSS), the frictional drag force exerted by flowing blood. In the human circulatory system, CTCs encounter a wide range of fluid dynamics: fluid shear stress ranges from low, highly fluctuating values in the microvasculature ($< 1 \text{ dyn / cm}^2$) to moderate levels in the venous system ($1\text{-}10 \text{ dyn / cm}^2$), and reaches extreme peaks in the arterial circulation ($10\text{-}30 \text{ dyn / cm}^2$, and up to 100 dyn / cm^2 in large arterial bifurcations). This intense hydrostructural stress acts as a highly efficient eliminator of circulating tumor cells, destroying more than 99% of monomeric CTCs within hours of entry into circulation. The rapid frictional forces can physically tear the plasma membrane of unadapted cells, inducing mechanical lysis, or trigger rapid anoikis, a form of programmed cell death induced by the loss of anchorage to a solid substratum. To survive this hostile mechanical environment, metastatic CTCs utilize specialized mechanosensitive ion channels and cell-surface receptors to convert fluid shear stress into active biochemical survival signaling. When subjected to fluid flow, the plasma membrane undergoes local tension changes that activate the mechanosensitive calcium channel TRPV4 and stretch-activated integrins. The resulting influx of extracellular calcium activates downstream cascades that stimulate the Hippo signaling pathway effector YAP. Activated YAP translocates to the nucleus, where it drives the transcription of a battery of anti-apoptotic genes and cytoskeleton-stabilizing factors, or induces a protective, reversible cell-cycle arrest. By temporarily halting proliferation and rigidifying their cortical actin cytoskeleton, surviving CTCs withstand high fluid shear forces during systemic transit.

Monomeric CTCs vs. multicellular clusters: Mechanical shielding and scaffolding

While CTCs frequently travel as solitary cells, they can also enter the circulation as cohesive multicellular formations

known as CTC clusters. Clinical and experimental data demonstrate that CTC clusters possess immensely higher metastatic potential than single CTCs, exhibiting a 20- to 50-fold higher efficiency in successfully seeding secondary tumors (Aceto, 2014; Chen *et al.*, 2022). This dramatic increase in metastatic capacity is directly linked to the distinct mechanical advantages inherent to collective cell biology. Below Figure 2 shows the mechanical shielding architecture of multicellular CTC clusters.

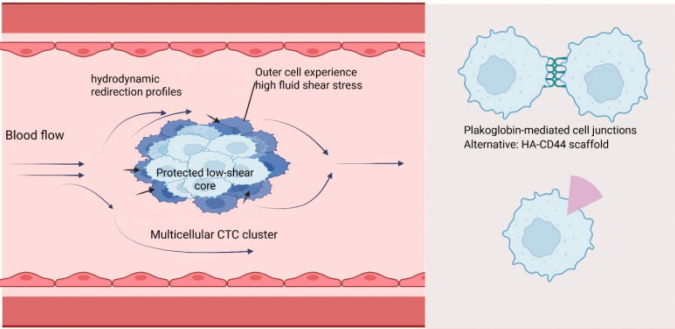


Figure 2. Mechanical shielding architecture of multicellular CTC clusters. Cross-sectional mapping tracking hydrodynamic redirection profiles. Outer boundary tumor shells systematically dissipate continuous kinetic fluid stress vectors to preserve the low-shear inner core region

The primary biophysical benefit of clustering is collective mechanical shielding from fluid shear stress. Within a circulating cluster, the peripheral cells bear the brunt of the hydrodynamic drag and frictional forces. By absorbing this mechanical energy, the outer cell layer creates a protected, low-shear core that shields the interior tumor cells from physical deformation and lysis. Furthermore, cells within a cluster maintain continuous cell-cell contact, completely bypassing the physical triggers of anoikis and preserving endogenous survival signaling pathways. Below Table 1 summarizes features of monomeric CTCs and multicellular clusters.

Table 1. Biomechanical comparison of monomeric CTCs vs. multicellular clusters

Biomechanical parameter	Monomeric CTCs	Multicellular CTC clusters	Primary references
Shear stress vulnerability	Extremely high; prone to rapid membrane rupture and mechanical lysis.	Low; peripheral layer absorbs hydrodynamic drag to protect inner core.	Krog & Henry (2018); Yang et al. (2024)
Survival signaling profile	High rate of anoikis due to complete loss of matrix anchor.	Sustained cell-cell juxtacrine signaling bypasses anoikis checkpoints.	Aceto et al. (2014); Schuster et al. (2021)
Primary scaffolding mechanism	None	Adherence junctions (Plakoglobin) or alternative Hyaluronic acid (HA) wraps.	Bobkov et al. (2026); Aceto et al. (2014)
Vascular arrest target	Active receptor-ligand engagement.	Combined high-probability capillary wedging & multi-receptor adhesion.	Au et al. (2016); Follain et al. (2018)
Relative metastatic potential	Baseline	20- to 50-fold elevation in secondary tumor seeding capacity.	Aceto et al. (2014); Chen et al. (2022)

Intercellular cohesion within these clusters is traditionally mediated by classic Adherence Junction (AJ) proteins. The desmosomal cell-junction component plakoglobin is highly expressed in clustered CTCs. Experimental knockdown of plakoglobin drastically destabilizes cell-cell adhesion, disrupts cluster integrity under fluid flow, and significantly suppresses lung macro-metastasis in vivo (Aceto *et al.*, 2014). However, in highly aggressive, poorly differentiated malignancies, such as triple-negative breast cancer (TNBC), classic AJ proteins are often genetically or epigenetically downregulated as part of a complete EMT program. In these contexts, tumor cells adapt by utilizing extracellular matrix components, specifically high-molecular-weight hyaluronic acid (HA), as an alternative extracellular scaffolding meshwork. This dense pericellular

HA coat acts as a chemical and structural glue, non-covalently crosslinking CD44 receptors on adjacent tumor cells to maintain robust structural cohesion under high arterial fluid flow (Bobkov *et al.*, 2026).

Arrest and adhesion: Overcoming hydrodynamic drag

Hemodynamics, permissive flow velocity, and spatial boundaries

Following systemic transit through the circulation, CTCs must arrest on the vessel wall and establish stable physical contact with the vascular endothelium before they can initiate extravasation. *Arrest* defines the initial physical transition of a rapidly moving tumor cell from convective transport within the bulk blood flow to a locally stationary vascular site. This process occurs via two distinct mechanisms: passive mechanical occlusion within capillaries whose internal lumens are smaller than the cell diameter, or localized deceleration within specific macro-vascular zones where local hemodynamic forces drop sufficiently to permit molecular interactions with the vessel wall (Au *et al.*, 2016; Follain *et al.*, 2018). For an arrest to become permanent and structurally viable, the CTC must convert initial contact into *adhesion*, the formation of specific, stable molecular attachments to the endothelial cell surface that generate sufficient mechanical force to resist hydrodynamic drag and fluid shear stress. Quantitative experimental models demonstrate that stable adhesion requires highly specific, permissive hemodynamic thresholds. Efficient, receptor-mediated stable adhesion is strictly favored in narrow flow velocity windows between 400 m/s and 600 m/s. If blood velocity exceeds 600 m/s, high hydrodynamic drag tears initial molecular bonds before they can mature. Biophysical force measurements reveal that an initial stabilization force of approximately 80 pN is required to anchor a tumor cell against blood flow. Within minutes in vivo, these adhesion forces scale up to exceed 200 pN.

Spatial confinement and nuclear deformability checkpoints

Vascular geometry dictates the precise anatomical sites where CTCs arrest. The probability of a CTC undergoing mechanical arrest is highly elevated at specific geometric landmarks, including narrow capillary beds, complex vessel bifurcations, and arterio-venous junctions. Within narrow vessels, CTCs can either squeeze through or become occluded. Experiencing spatial confinement or partial occlusion slows the cell body down, temporarily trapping it against the endothelial wall, which increases the probability of ligand-receptor engagement. This spatial checkpoint depends on the deformability of the whole tumor cell and its nucleus.

The nucleus remains the primary physical obstacle; if the nucleus and cytoplasm can deform sufficiently, the CTC can pass through the microvascular restriction and continue circulating systemically. If nuclear deformation is limited by high lamin A/C expression, the cell becomes physically occluded, increasing endothelial contact area and favoring molecular adhesion - see Figure 3 below.

Mechanics of receptor-ligand adhesion and binding dynamics

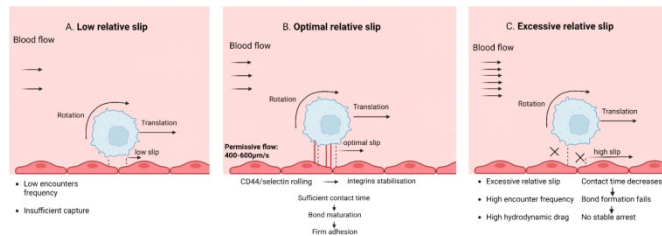


Figure 3. Hydrodynamic slip mechanics during endothelial contact. Comparative structural dynamic panels contrasting cell capture efficiency as a function of local velocity variations. Highly regulated velocity cross-sections enable catch-bond development to initiate firm anchoring

Adhesion depends on the binding dynamics of receptor-ligand pairs operating under non-equilibrium shear flow. Under fluid flow, CTCs undergo complex translational rolling and rotational slipping motions along the endothelial wall. As the relative slipping velocity increases, cell-surface receptors and endothelial ligands encounter each other at an increased frequency, but each individual molecular encounter lasts for a shorter duration. Consequently, the molecular binding rate initially increases with relative velocity, driven by the higher encounter frequency, before plateauing and dropping when the shortened contact duration fails to allow bond formation. To achieve arrest under these dynamic conditions, tumor cells utilize a multi-step adhesion cascade where early, transient rolling interactions are initiated by CD44 receptors and selectins, followed by structural stabilization via β_1 -integrin and $\alpha_v\beta_3$ -integrin.

Extravasation: Transendothelial migration and barrier disruption

Flow-mediated and signalling-driven endothelial remodelling

Extravasation is the complex process by which a stably arrested CTC crosses the vascular endothelial wall to enter the surrounding parenchymal tissue. Successful extravasation requires coordinated mechanical modifications in both the endothelial barrier and the invading tumor cell. The endothelium must actively remodel its junctional architecture to open a physical path for transmigration, while the tumor cell must deform its body and nucleus to pass through the vessel wall. Endothelial remodeling is regulated by two distinct inputs: the mechanical forces of blood flow combined with the physical presence of the arrested cell, and downstream molecular signaling cascades. Following stable CTC arrest, blood flow continues to act on both the endothelium and the immobilized tumor cell, providing mechanical cues that drive vascular remodeling. In response, the endothelial wall forms localized pockets and membrane protrusions that progressively wrap around and encapsulate the tumor cell. Experimental

models show that if blood flow slows down or is surgically arrested, this endothelial remodeling and subsequent tumor cell extravasation cease. This flow-dependent remodeling requires active endothelial cooperation: endothelial cells must convert mechanical shear inputs into intracellular transcriptional signaling. Fluid flow alters the transcriptional state of the endothelium; under a physiological blood flow velocity of 400 m/s, the expression of the vascular endothelial growth factor receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4) is upregulated, with VEGFR2 showing the most pronounced increase. Figure 4 visualizes it below.

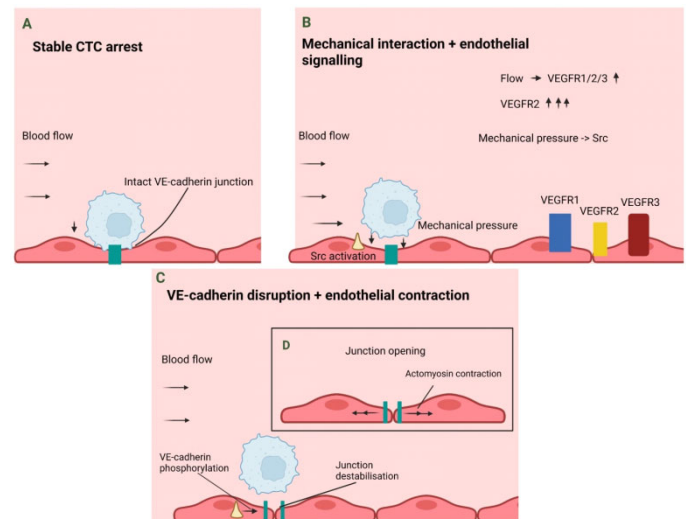


Figure 4. Signaling events during endothelial junction disruption. Step-by-step schematic showing how endothelial boundaries open a paracellular migration gap in response to physical tumor cell interactions

Simultaneously, the arrested CTC acts on the endothelial cells through combined mechanical and biochemical signaling. The physical pressure of the tumor cell activates endothelial Src-dependent signaling pathways. Activated Src phosphorylates VE-cadherin (Vascular Endothelial cadherin) at key cytoplasmic residues, inducing partial junctional disassembly and weakening the mechanical adhesion between neighboring endothelial cells (Aragon-Sanabria *et al.*, 2017). Concurrently, the endothelial actin-myosin cytoskeleton generates contractile forces that pull the cell edges outward, producing a transient paracellular gap through which the deformed tumor cell can pass.

Therapeutic horizons and future perspectives

Understanding the mechanobiology of the metastatic cascade opens novel therapeutic strategies aimed at targeting the physical vulnerabilities of migrating tumor cells. Rather than focusing solely on biochemical inhibitors, modern oncology can exploit these mechanical filters to prevent metastatic spread. Promising mechanotherapeutic avenues include:

- **Targeting EMT-associated regulators:** Small-molecule inhibition of Snail or Twist1 can be utilized to prevent the cytoskeletal fluidization and alterations in nuclear compliance required for intravasation and extravasation, trapping tumor cells in a rigid, non-migratory state.
- **Disrupting CTC cluster cohesion:** Pharmacological targeting of plakoglobin or hyaluronic acid (HA) scaffolding (e.g. via hyaluronidase formulations) can break apart circulating tumor cell clusters into single cells,

exposing them to lethal fluid shear stress and destroying their protective microenvironment.

- **Modulating integrin activation states:** Therapeutics targeting the conformational activation of β_1 and $\alpha_v\beta_3$ integrins can prevent arrested CTCs from establishing stable, high-force (>200 pN) adhesions with the endothelium, leaving them vulnerable to hydrodynamic clearance.
- **Endothelial Junctional stabilization:** Small molecules that inhibit Src-dependent VE-cadherin phosphorylation can lock endothelial junctions, preventing the formation of paracellular gaps and blocking tumor cell extravasation.

Conclusion

The metastatic cascade is a demanding physical journey governed by highly stringent mechanical selection pressures and filters. By examining metastasis through a mechanobiological lens, it becomes clear that tumor cell survival and successful secondary colonization depend on structural and biomechanical adaptations. From resisting compressive stress and adapting via EMT in the primary tumor, to enduring fluid shear stress via multicellular clustering in the circulation, and utilizing integrin-mediated mechanotransduction to achieve stable arrest and extravasation, physical forces shape every stage of cancer progression. Quantifying these physical properties, such as the balance of forces required for nuclear deformation or the permissive hemodynamic velocities required for endothelial remodeling, deepens our understanding of cancer biology and establishes mechanobiology as an essential framework for discovering novel therapeutic targets to combat metastatic disease.

Acknowledgement

The authors would like to thank Joe Choo-Choy for the helpful discussions.

Declarations

Author contributions

Anastasiia Korolenko: Conceptualization, Writing – original draft preparation, Visualization, Joe Choo-Choy: Conceptualization, Writing – review and editing, Visualization, Tamas Kovacs: Supervision, Writing – review and editing, Project administration.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

Data availability statement

No datasets were generated or analysed during the current study. All information and quantitative parameters synthesized in this review are derived from published peer-reviewed articles cited in the references list.

Ethics Approval

Not applicable. This manuscript is a review article and does not report on primary data involving human participants, human clinical tissue samples, or animal experiments.

REFERENCES

- Aceto, N., et al. (2014). Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell*, 158(5), 1110-1122.
- Aragon-Sanabria, R., et al. (2017). VE-Cadherin Disassembly and Cell Contractility in the Endothelium are Necessary for Barrier Disruption Induced by Tumor Cells. *Scientific Reports*, 7, 45835.
- Au, S. H., et al. (2016). Clusters of circulating tumor cells traverse capillary-sized vessels. *Proceedings of the National Academy of Sciences*, 113(12), 3209-3214.
- Bobkov, I., et al. (2026). Hyaluronic acid substitutes for adherence junctions as clustering scaffolds in aggressive triple-negative breast cancer. *Journal of Cell Biology*, 225(2), e20250812.
- Chen, L., et al. (2022). A narrative review of circulating tumor cells clusters: A key morphology of cancer cells in circulation promote hematogenous metastasis. *Annals of Translational Medicine*, 10(6), 365.
- Dattani, S., et al. (2024). Global Cancer Mortality and All-Cause Mortality Dynamics. *Our World in Data / Lancet Oncology*, 12(3), 201-215.
- Follain, G., et al. (2018). Hemodynamic Forces Tune the Arrest, Adhesion, and Extravasation of Circulating Tumor
