

Research

Membrane Biophysics-Based Mechanisms of Cancer Progression: the Active Decoupling/ Vanguard Hypothesis

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Abstract:

Accumulating evidence indicates that the complex intra and intercellular infrastructure composed of membranous nanostructures—including tunneling nanotubes (TNTs), and extracellular nanoparticles (EPs) — serve as a critical physical determinant of cancer progression, metabolic rewiring, and therapy potential. Further, we hypothesize that the biogenesis and stability of these communication conduits are intrinsically linked with local membrane composition and physical properties. Pathological alterations in lipid and protein shape, and therefrom induced changes in membrane free energy may favour spontaneous membrane budding and subsequent tubule elongation or shedding extracellular vesicles (EVs). Because malignant nanostructures depend on these permissive physical landscapes, we propose that disrupting this physical network represents a viable oncology frontier. Specifically, therapeutic manipulation of the host membrane composition via externally added membrane curvature-modulating compounds, amphiphilic molecules, or membrane-active agents, can alter membrane properties and destabilize and collapse the tumor's intra and intercellular infrastructure, presenting a novel, mutation-independent strategy to halt cancer invasion.

Keywords: Cancer; Cellular infrastructure; Tunneling nanotubes; Extracellular vesicles; Extracellular particles; Cancer theranostics

1. Introduction

Early description of breast cancer was recorded already on ancient Egyptian medical texts cca 2500 BC (Hajdu, 2016). It concluded that the disease had no treatment. Since then, considerable progress has been made, and lifetime cured cases are registered (Wagle et al., 2025). However, the underlying mechanisms are not yet completely understood. As tumors are composed of cells, it is necessary to study the features at the cellular and subcellular levels. Extensive study has been devoted to genetic mechanisms of cancer progression, but recently, highly curved membranous nanostructures have also become a subject of increasing interest. Membranes are not just passive bags; they are active, mechanosensitive physical landscapes. Tunneling nanotubes and extracellular particles are involved in intercellular communication and are potentially important players in cancer progression (Kralj-Iglič et al., 2012). We argue that cancer progression is fundamentally driven by biophysical alterations of cellular membranes, in particular, of membranous nanostructures that serve as vectors for metabolic, structural and signaling advantages.

2. Tunneling nanotubes as the cell infrastructure

A landmark experimental research (Iglič et al., 2003) provided direct evidence of phospholipid nanotubes acting as platforms for the traveling of localized vehicles to ferry enclosed solutions between different membrane-enclosed compartments (**Figure 1A**). The gathered experimental evidence indicated that these nanoconduits are present in archaea, bacteria, plants, and mammals (Gozen and Dommersnes, 2020). While the intercellular communication by tunneling nanotubes has been acknowledged (Rustom et al., 2004; Veranič et al., 2008), it was hypothesized that membranous structures, in particular the nanotubes, are also present inside the cells where they may direct the transport of material between the compartments (Iglič et al., 2003).

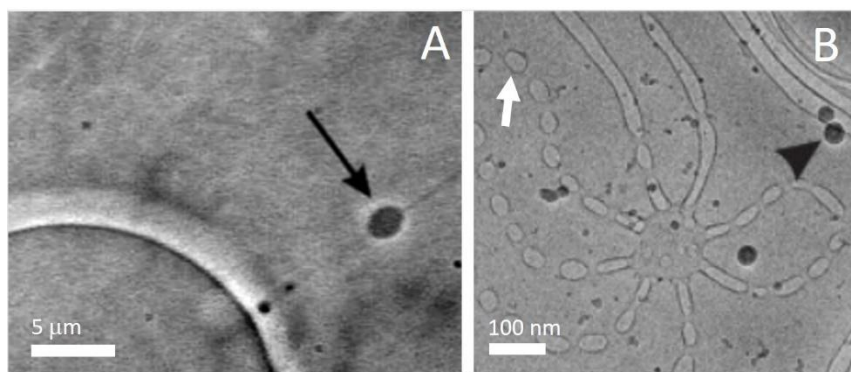


Figure 1A: Phase contrast optical microscope image of directed transport along the phospholipid nanotube by a gondola (black arrow). From (Iglič et al., 2003), with permission; **B:** Cryogenic electron microscope image of tubular to globular (white arrow) shape transition in phospholipid membrane. Black triangle points to an electron-dense particle. From (Spasovski et al., 2024, CC BY-NC 4.0 license). Under a phase contrast microscope, optical diffraction effects and phase halos artificially broaden the visual silhouette of the tube, making it appear significantly thicker in the image than it is in physical reality.

3. Deviatoric elasticity – a hallmark of stability of the membranous nanostructure shape

To mathematically and physically explain how a cell can maintain a directed nanotube infrastructure instead of breaking down into random, wandering spherical vesicles, we must look at deviatoric elasticity (also frequently referred to in membrane biophysics as the anisotropic bending elasticity or the spontaneous curvature anisotropy of lipid bilayers) (Kralj-Iglič et al., 2020). Standard membrane theories (like the Helfrich spontaneous curvature model) treat the lipid bilayer as an isotropic, fluid sheet (Helfrich, 1973). However, real biological membranes are packed with anisotropic components—such as elongated proteins, asymmetric lipids, and oriented cytoskeletal attachments. Deviatoric elasticity accounts for the physical reality that these molecules bend differently in one direction than they do in another and can – as they are free to rotate – undergo

orientational ordering. This represents another degree of freedom of the system and can lower the free energy of the membrane. On the spherical parts, there is no orientational ordering of the membrane constituents as all directions are equivalent. On the tubular parts, however, orientational ordering lowers the membrane free energy, depending on the tube diameter, and if the membrane contains anisotropic constituents with the diameter of the tube small enough, prefer the tubular shape over the globular one (Kralj-Iglič et al., 2002; Kralj-Iglič et al., 2020).

4. In tumour, cell size and integrity are intricately linked

In some malignancies, the cells are much smaller than a typical healthy cell of that tissue type (Shashni et al. 2018, Jiang et al., 2017). In a normal cell, the nucleus is small and takes up a minor fraction of the total cell volume. Even if a cancer cell shrinks to a small overall size, its nucleus remains large, resulting in a high nucleus-to-cytoplasm ratio—one of the most reliable visual triggers a pathologist uses to diagnose cancer.

One of possible reasons for small amount of cytoplasm could be that the cell is shrinking because it is actively casting off material. Cancer cells undergo constant membrane fragmentation preceded by budding. The cancer cell pushes out a piece of its plasma membrane, packs it with materials, and pinches it off (Zhu et al., 2021). If an aggressive cancer cell continuously pinches off thousands of microvesicles (ranging from 100 nm to large oncosomes up to 1 μ m, it is constantly bleeding out its own plasma membrane and cytoplasm (Guzowska et al., 2026). Unless it can regenerate its cytoplasm at the exact same rate, the cell will physically shrink. This leaves behind a stripped-down, streamlined cell with a disproportionately large nucleus. If a malignant cell excessively sheds extracellular particles, its total cytoplasmic volume decreases over time, leaving a physically smaller mother cell with a relatively large nucleus.

The high nucleus-to-cytoplasm ratio characteristic of highly metastatic cancer cells may not be merely a consequence of rapid cell division, but an active manifestation of hyper-vesiculation. Malignant cells reduce their cytoplasmic volume by aggressively shedding extracellular vesicles and large oncosomes; this mass extrusion simultaneously de-bulks the parent cell for streamlined amoeboid migration while biochemical weaponizing the local and distant microenvironments to drive efficient metastasis.

If a cell has a small amount of cytoplasm because it has aggressively shed its mass into the environment, that cell is statistically much more dangerous and metastatic. The fragments it leaves behind serve as a vanguard force for tumor spread. The cytoplasm lost by the cancer cell is often packed with immunosuppressive proteins and signaling RNAs. As these fragments drift away, they exhaust and paralyze local T-cells and natural killer cells, creating a safe zone for the tumor (Lucotti et al., 2022). The shed particles travel through the bloodstream ahead of the cancer cell. They land in distant organs (like the lungs or liver) and forcefully reprogram the local tissue to make it welcoming for when the shrunken parent cell eventually arrives.

5. Destruction of the tumor from within

When a solid tumor grows past a certain diameter (typically around 2 to 4 millimeters), it outstrips its local blood vessel supply (Lee et al., 2018). Cells at the leading edge are often physically smaller in cytoplasmic volume than healthy epithelial cells, retaining a highly prominent, large nucleus. They are small because they are metabolically hyperactive. They actively shed their cytoplasm in the form of extracellular vesicles and large oncosomes forward into the healthy tissue (Deisboeck et al., 2006). They consume all the incoming oxygen and glucose, leaving the cells deep in the center to starve in a state of severe hypoxia (oxygen deprivation). On the border of the necrotic core, cancer cells avoid death by using autophagy to shrink their cytoplasmic volume, while actively fragmenting off microvesicles. In the starved center, without oxygen and glucose, they cannot generate ATP. Their membrane pumps fail, causing water to rush into the cells. These starving cells swell up to a much larger, unstable size. Because the cell continues to expand without metabolic control, the outer membrane loses all structural integrity, and ruptures. Unregulated, catastrophic fragmentation of cancer cells takes over via a specific form of cell death. The cell fragments into unstructured debris, spilling its raw contents directly into the tissue and releasing pro-inflammatory cellular debris that triggers tumor-promoting inflammation (Lee et al., 2018).

6. Integrity of tissue

In healthy epithelial tissues, E-cadherins (Epithelial Cadherins) are transmembrane glycoproteins that serve as the primary molecular adhesive holding cells together (Li et al., 2012). They act as a structural anchor that establishes tissue architecture, maintains cell polarity, and regulates intercellular communication. In solid tumors (particularly carcinomas), the down-regulation, loss, or functional inactivation of E-cadherins is a definitive hallmark of progression (Baskar Vimala et al., 2025). From a purely physical perspective, uncoupling E-cadherins from the cortical actin cytoskeleton removes the structural tension that keeps the cell membrane flat and stable. The bending rigidity of the lipid bilayer drops significantly. The internal actomyosin contractile machinery becomes unconstrained, causing the unanchored plasma membrane to undergo continuous, localized budding. This mechanical instability increases the frequency of membrane fission events, causing the cell to shed massive quantities of EPs into its surroundings. Without E-cadherins to hold them back, cells at the tumor surface can break away. They don't always detach as single cells; instead, they often break off in multicellular fragments or clusters (Circulating Tumor Cell clusters). These fragmented clusters are highly lethal. Because the cells inside the cluster still retain some internal cell-to-cell contact, they protect each other from dying in the bloodstream, possessing up to 100 times higher metastatic potential than single wandering cancer cells. The loss of E-cadherin does not just let the cell float away; it triggers an internal biochemical chain reaction that directly accelerates the micro-fragmentation (shedding) of the cytoplasm. Normally, the tail end of E-cadherin binds to a signaling protein called beta-catenin inside the cell. When E-cadherin disappears, beta-catenin is liberated and rushes into the cell's nucleus, turning on genes that completely dismantle the rigid, organized cytoskeleton (Gloerich et al., 2017). Without the structural framework of E-cadherins maintaining a flat, stable cell shape, the plasma membrane becomes highly unstable and fluid. The internal contractile forces (driven by the RhoA/ROCK pathway) are unleashed. The cell begins to violently bubble and bleb, shifting its metabolism into overdrive to pump out extracellular vesicles and large oncosomes (Gaptulbarova et al., 2024). The cell loses its wide, flat epithelial shape because E-cadherins are no longer stretching it against its neighbors. It balls up into a smaller, rounded, fluid shape (Alhalhooly et al., 2021). As it rolls or crawls away, the unstable, unanchored membrane allows it to rapidly shed its vanguard vesicles forward into the tissue. The cell physically deflates its cytoplasmic volume while keeping its large, genetically packed nucleus intact.

7. The Active Decoupling / Vanguard hypothesis

We hypothesize that in normal homeostasis, intracellular and intercellular transport is directed and energetically passive, occurring via localized dilatations moving along a continuous infrastructure of phospholipid nanotubes driven by membrane tension gradients (**Figure 1A**). In malignancy, this structural infrastructure becomes highly defective due to the cytoskeletal uncoupling associated with E-cadherin loss. Unable to maintain internal directed transport, the cell undergoes localized membrane accumulation, forcing a transition from internal dilatation-mediated routing to chronic, external membrane budding and fission. This infrastructural collapse drives the net loss of cytoplasmic volume, generating the characteristic high nucleus-to-cytoplasm ratio while generating the vanguard extracellular particles.

The membrane contains elongated, anisotropic proteins (such as BAR-domain proteins, oriented tubulin/actin complexes, or asymmetric membrane-spanning inclusions). These molecules have a distinct preference for in-plane orientation in the membrane. They better fit into a cylinder than into a globule, but are physically strained due to geometrical constraints. When these anisotropic components align themselves along the circumference of a nanotube, the system hits a state of low membrane free energy. The orientation of the molecules perfectly matches the highly asymmetric physical shape of the cylinder. If a thermal fluctuation or an external force attempts to pinch that nanotube down into a series of detached, round globular vesicles would inflict a massive deviatoric energy penalty. As long as the deviatoric bending modulus is sufficiently high, this energy barrier physically locks the membrane into its cylindrical nanotube state. It structurally forbids the fission process that would otherwise slice the nanotube into a chaotic cloud of wandering vesicles.

The normal cell synthesizes and perfectly organizes the anisotropic, membrane-shaping proteins (and their cytoskeletal anchors, heavily regulated by E-cadherin signaling). This generates a high deviatoric bending modulus, mechanically stabilizing a continuous, robust internal nanotube highway capable of directed cargo trafficking via localized dilatations – gondolas (**Figure 1A**). Because of this energy barrier, the network cannot easily degrade into globular vesicles, ensuring directed, energy-free transport along the continuous infrastructure. In cancer cells, the infrastructure becomes defective. The loss of E-cadherins and the resulting cytoskeletal disassembly disorganizes or downregulates these specialized anisotropic molecules. The deviatoric stabilization collapses. Lacking this directional elastic protection, the membrane loses its cylindrical stability and spontaneously breaks down into isotropic, globular vesicles via unchecked budding and fission, driving the mass-shedding state of the Vanguard Hypothesis (**Figure 1B**).

8. Therapeutic implications based on the Active Decoupling / Vanguard Hypothesis

Because membrane self-assembly is fundamentally reversible, therapeutic strategies aimed at restoring E-cadherin expression or stabilizing the cortical actin skeleton could theoretically re-establish the critical force thresholds and deviatoric elasticity required to rebuild the cell's internal nanotubular infrastructure. Artificially forcing the restoration of this continuous directed transport network would effectively reverse the mass-transport imbalance, halting the hyper-vesiculation of vanguard particles and freezing the cell's metastatic capacity. This concept opens up a profound new angle for therapeutic prophylaxis. If the destruction of the infrastructure is what drives metastasis, then cancer therapy should focus on stabilizing the nanotubular network.

9. Conclusions

In practice, repairing a defective nanotubular infrastructure can be achieved through a multi-modal biophysical intervention. Combining small-molecule epigenetic agents (to restore the E-cadherin/ β -catenin actin anchors) with intravenously delivered BAR-domain biomimetic nanoparticles could restore both the pulling mechanics and the anisotropic deviatoric elasticity required to stabilize cylinders. When coupled with acoustic microenvironmental tuning to optimize lateral membrane tension, this combined approach physically suppresses the transition from continuous internal transport to irreversible external fission. This effectively freezes the mass-transport imbalance driving the Vanguard Hypothesis and stops metastasis at a purely mechanical level.

Conflicts of Interest: The author declares no conflict of interest.

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