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REVIEW

Tunneling nanotubes and cytonemes in cancer and development

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Embryonic, adult, and cancer cells can exchange cytoplasmic proteins and even organelles using long, slender nanotubular interconnections. These cytoplasmic extensions, termed cytonemes, tunneling nanotubes, or tumor microtubes, span a spectrum of sizes. They have a structural core of F-actin filaments and can transport proteins and organelles ranging in size from small vesicles to mitochondria. These nanotubular interconnections can support embryonic development and tissue-tissue interactions as well as cancer cell defense against hypoxia, metabolic stressors, and chemotherapy. For example, tunneling nanotubes can transfer mitochondria to immune cells from non-malignant or tumor cells to promote or disable tumor cell killing. Numerous molecules initiate and maintain these nanotubular structures, suggesting cell type specificity. Many unanswered conceptual and mechanistic questions remain concerning the molecular and regulatory mechanisms driving their generation, structural and cell type–specific versus universal properties, and potential for novel therapeutic interventions—all providing exciting new opportunities in this rapidly expanding field of cell biology.

Introduction

Like people, cells communicate with each other in many different ways. Face-to-face sharing of information can occur via cellular gap junctions, public speaking can be accomplished by emitting growth factors and cytokines, and personal objects can be mailed using extracellular vesicles and endocytosis (Alberts et al., 2022). Interestingly, just as the establishment of telephone lines permitted direct, private communication between people at long distances, cells can also generate direct interconnections to distant cells or tissues for the focused transfer of information and cellular contents using long, slender membrane tubes termed cytonemes or tunneling nanotubes (TNTs). Even social media can be mimicked by certain cells that establish a TNT-mediated network of interconnections between multiple cells.

These thin membranous tubules have been termed cytonemes, TNTs, TNT-like structures, tumor microtubes, membrane nanotubes, nanotubular networks, and related names in over a thousand publications (Cervantes and Zurzolo, 2021; Dagar et al., 2021a; Osswald et al., 2015; Pinto et al., 2020; Rustom et al., 2004; Wang and Gerdes, 2015; Watson et al., 2023; Yamashita et al., 2018). These direct nanotubular cellular interconnections (Box 1) can transfer a wide range of cytoplasmic contents from 1 cell to another distant cell. Depending on the type of nanotubular link, they can transfer molecules ranging in size from small ions, including calcium fluxes, to larger growth factors, vesicles, and even mitochondria (Figs. 1 and 2). In this review, we primarily discuss TNTs in comparison to cytonemes and other tubular structures and review their roles in cancers, other diseases, and embryonic development, focusing on recent intriguing primary publications alongside some classical studies. Finally, we discuss eight unresolved classes of broad conceptual or specific functional issues that should provide abundant exciting opportunities for future research.

Cytonemes and TNTs

Cytonemes are extensively studied nanotubular cytoplasmic extensions that interconnect cells to mediate intercellular signaling (Fig. 1 and Fig. 2 A), particularly during embryonic development (Table S1 [Hall et al., 2024; Ma et al., 2025; Wang et al., 2025b]). A wide range of developmental regulators can be targeted to other cells via cytonemes to regulate tissue patterning and differentiation. Cytonemes in *Drosophila* that transport the TGF-β family member DPP (decapentaplegic) were originally shown to require, besides actin, the expression of multiple genes including a formin, cell adhesion proteins (neuroglian and capricious), and a dynamin (Roy et al., 2011). Since then, other molecules have been implicated in cytoneme structure and their intercellular transport function, including Wnt, Notch, and fibroblast growth factor receptors (Hu et al., 2024; Ma et al., 2025; Patel et al., 2022; Sherer and Mothes, 2008; Yamashita et al., 2018).

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Box 1. **General definitions and comparisons**

Filopodia: Slender, laterally motile cellular protrusions ∼200–400 nm in diameter and usually 2–10 µm in length with a core of F-actin. Filopodia are often observed in migrating cells. They have a closed membranous end that does not interconnect cells or mediate signaling. Their functions are reported to include sensing the microenvironment, guiding cell migration, and sometimes adhesion to the substrate.

Long filopodia: Filopodia that are 200–500 nm in diameter but substantially longer than standard filopodia that can extend as far as 20–150 µm. They may be used for distant probing or contact and potentially for contractility between tissues.

Cytonemes: Slender closed-ended interconnections between cells ∼50–200 nm in diameter with F-actin cores, though they can display localized bulges, e.g., if they contain mitochondria. They are usually 10–100 µm in length as they extend from one cell to another to transport ions, signaling proteins, and occasionally mitochondria. Cytonemes are most frequently reported during embryonic development with roles as signaling conduits by transferring regulatory proteins to target cells.

Tunneling nanotubes: Slender cell interconnections ∼50–400 nm in diameter that can extend 10–100 µm between cells containing F-actin, microtubules, and sometimes intermediate filaments that can transport and transfer cargo including ions, proteins, vesicles, other organelles, and/or mitochondria. They can be either open-ended or closed-ended. "Thick tunneling nanotubes" can be substantially thicker, roughly 700–1500 nm, often due to parallel arrangements of bundled individual tunneling nanotubes.

Tumor microtubes: Larger cell-cell interconnecting tubules of tumor cells that are 1–2 µm in diameter, though wider in some cancers. They can extend tens to hundreds of micrometers to form networks between cancer cells or with other cells. They are used for cell-cell signaling, organelle exchange, and resistance to stressors including hypoxia and chemotherapy.

Note: The dimensions listed here are usual reported averages. The functions listed can vary for each structure according to differences in cell/tissue type and biological status. For example, tunneling nanotubes can exist in embryonic development, mature tissues, and tumors with potentially differing functions. Additionally, publications in the field appear to use varying terminologies for similar structures, e.g. labeling very similar nanotubular structures of cancer cells as tunneling nanotubes, TNT-like structures, or tumor microtubes depending on the research group.

Cytonemes have been particularly well-characterized in *Drosophila*, but they also perform critical functions in mammalian systems. For example, during mouse neural tube development, cytonemes were shown to be essential for generating normal neural tubes (Hall et al., 2024). Long cytonemes are reportedly generated through myosin-X (MYO10) activity, and they transport critical developmental signaling molecules including sonic hedgehog and Wnt for the regulation of neural cell fate during neural tube patterning. Cytonemes are also required for Notch-mediated epidermal patterning and differentiation in zebrafish (Wang et al., 2025b).

TNTs and TNT-like structures are also long tubular membranous structures, but they are generally larger in diameter than cytonemes (Fig. 1 and Fig. 2 B)—approximate diameters are 50–400 nm for TNTs versus 50–200 nm reported for cytonemes, but with considerable overlaps in size (Cervantes and Zurzolo, 2021; Dagar et al., 2021a; Hu et al., 2024; Jung et al., 2020; Korenkova et al., 2020; Lou et al., 2024; Sherer and Mothes, 2008; Yamashita et al., 2018). Both TNTs and cytonemes can sometimes extend large distances—in some cases up to 500 µm or more between cells for large TNTs termed tumor microtubes. *In vitro* studies describe two distinct mechanisms by which TNTs are generated: either by the extension of a slender cell process outward to contact and then to interconnect with another cell or by the generation of residual thin cellular fibers as cells separate from one another (Ljubojevic et al., 2021; Matejka et al., 2024).

TNTs can be homotypic or heterotypic: homotypic TNTs link cells of the same type, such as neuronal cells in a network, whereas heterotypic TNTs provide nanotubular connections between different cell types (Cervantes and Zurzolo, 2021). Homotypic TNTs can provide coordination between related cells, such as within a tumor for protection against stressors such as hypoxia (Desir et al., 2016), whereas heterotypic TNTs can link distinct cell types, for example, between cancer and immune cells for mitochondrial transfer (Ikeda et al., 2025). Some TNTs are "closed-ended" in that they are open at one end but closed at the other end by a gap junction containing connexin 43 at the target cell surface to permit the transfer of small molecules. In addition, TNTs have been described as "thin" or "thick" depending on their diameter of ∼50–400 nm for thin TNTs and 700–1,500 nm for thick TNTs (Fig. 1).

TNTs can provide interconnections between not only normal, nonmalignant embryonic and adult cells, e.g., between neuronal and immune cells, but also between multiple other cell types (see following sections, Fig. 3, and Cervantes and Zurzolo, 2021). TNTs have been studied most intensively in cancer, especially in brain cancers but also in a broad range of hematologic and solid cancers, both *in vitro* and *in vivo* (Table S2). TNTs have also been implicated in the cell-to-cell transfer of pathogenic proteins and viruses. TNTs can overlap morphologically and conceptually with other intercellular transfer structures such as tumor microtubes (which are larger than thin TNTs), long filopodia, microtentacles, cytokinetic bridges, and membrane nanotubes (Cervantes and Zurzolo, 2021; Dagar et al., 2021a; Lou et al., 2024; Osswald et al., 2015).

Cytonemes and TNTs both contain a structural core of F-actin filaments. As depicted in Figs. 1 and 2, morphological studies of these nanotubular structures ranging from thin (50 nm) to thick tubules (1 µm or more) reveal that their contents can include a wide range of molecules and structures, including ions and proteins, microtubules, intermediate filaments such as vimentin, vesicles including autophagosomes, rough ER, and even mitochondria (Cervantes and Zurzolo, 2021; Jung et al., 2020; Lou et al., 2012; Wang et al., 2025a). Although classical filopodia lack vesicles and are shorter than cytonemes and TNTs, cellular extensions termed "long filopodia" and cytonemes can contain organelles including mitochondria—underscoring the overlap in contents between different cytoneme- or TNT-like structures (Matejka et al., 2024; Sartori-Rupp et al., 2019; Wood et al., 2021).

High-resolution microscopy revealed that classical *Drosophila* cytonemes can be initiated as very long filopodia that extend outward to contact invaginations in target cells and ultimately to interconnect them. Importantly, they can contain rough ER and even mitochondria in bulges of these long filopodia, though only

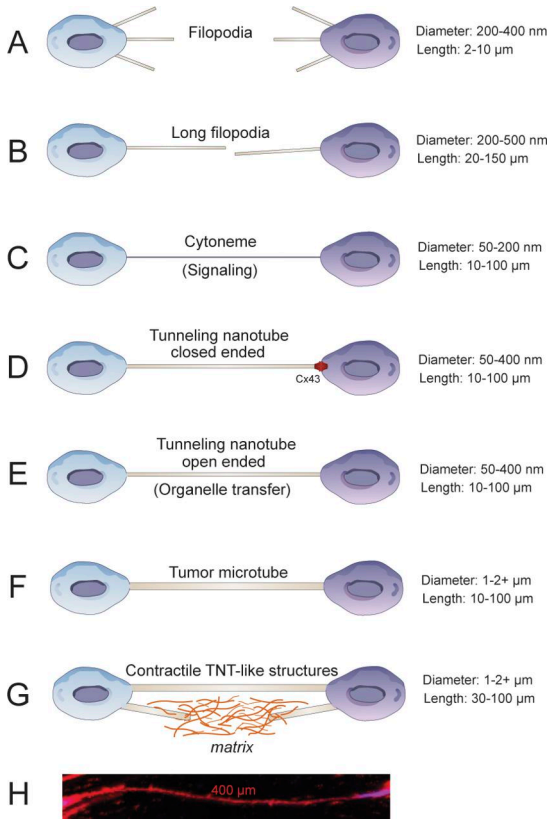

Figure 1. **Nanotubular cell–cell protrusions.** Schematic diagrams of long, slender cellular extensions that protrude from cells and can form long-distance interconnections with other cells. **(A–H)** They include (A) filopodia, (B) "long filopodia," (C) cytonemes, and (D) TNTs—which can be classified as either closed-ended with a terminal gap junction (red) at one end containing connexin 43 (Cx43) or (E) open-ended TNTs, which can in turn be classified as either thin or thick, with thick TNTs also termed (F) tumor microtubes, and (G) contractile TNT-like structures. The latter long, slender, contractile protrusions can contract extracellular collagen inward toward cells while translocating the cell body outward; but (H) they can also become long TNT-like structures (as shown here for cultured MDA-MB-231BO human breast cancer cells stained red for F-actin by ATTO 565 phalloidin and blue for nuclei by DAPI using confocal microscopy imaging by K. Yamada). Consequently, we speculate that these long contractile cell protrusions may be precursors of intercellular connections. The nomenclature for all these nanotubular structures can sometimes appear to differ confusingly when comparing different publications, which apply differing terms to the structures they characterize.

rarely vesicles (Wood et al., 2021). Some cancer cells, including breast cancer cells, can produce long, strongly contractile cell protrusions containing mitochondria, which suggests they might be different from filopodia and TNTs (Nazari et al., 2023). However, an ultrastructural study of a breast cancer cell line describes morphologically similar long filopodia suggested to be precursors to TNTs (Franchi et al., 2020), and some long filopodia have been shown to be contractile during embryonic development (Chauhan et al., 2009). Nevertheless, whether some TNTs are contractile remains to be determined. Fig. 1 depicts the full range of membranous tubular structures; it is, however, important to emphasize that their relationships with each other remain to be further elucidated. Although we speculate that long filopodia and the thick, long cell protrusions that extend outward from cells to contact and remodel surrounding extracellular matrix may potentially be precursors of thick TNT-like structures including tumor microtubes, this possibility needs direct experimental evaluation.

While the vast majority of studies have focused on characterizing TNT and cytoneme composition as well as their intercellular transfer functions, their biophysical roles in cell-to-cell physical interactions have been examined much less. A recent *in vitro* study characterized TNT stiffness and internal tension by atomic force microscopy, reporting that long thin TNTs displayed higher internal tension than shorter TNTs (Ota and Nagayama, 2025). We speculate that such forces between connected cells might promote their translocation. TNTs have been implicated in the compaction of spheroids of MCF7 cancer cells *in vitro* (Pulze et al., 2020), although whether their role depends on direct cell–cell forces or indirect effects of signaling is unclear. It is also not clear whether such biophysical interactions and nanotubular contractility play a significant role *in vivo*, e.g., by influencing the proximity of 1 cell to another, such as to promote cancer cell interactions with endothelial cells during extravasation or intravasation, or to pull immune cells toward their targets.

TNTs in embryonic development, adult organisms, and diseases

In vivo studies in zebrafish embryos demonstrate the importance of TNTs in normal embryonic development (Korenkova et al., 2025). TNTs in zebrafish embryos can transfer cytosolic proteins and organelles such as mitochondria and early endosomes to other migrating gastrula cells (Fig. 3 D). TNT-like extensions in migrating neural crest cells have been suggested to play a role in the directionality of the neural crest cell migratory stream (Teddy and Kulesa, 2004) (Fig. 3 A). Recently, TNT-like tubular interconnections have been identified as physical interconnections extending between cardiomyocytes of the myocardium through the cardiac jelly extracellular matrix to insert into endocardial cells in the endocardium for mediating long-distance communication needed for normal heart formation (Miao et al., 2025). These TNT-like structures depend on Cdc42 activity for their formation and can transport proteins such as signaling molecules and vesicles. For example, they permit developmental signaling via the Notch1 pathway. Disruption of these TNT-like linkages impairs myocardial morphogenesis (Miao et al., 2025). These studies of nanotubular structures in different embryonic systems suggest that the morphological and functional roles of cytonemes and TNTs can overlap.

In mature organisms, TNT interconnections between cells within a tissue or between cells of different tissues have been suggested to play roles in inter-tissue regulation. For example, TNTs can interconnect pericytes that surround capillaries in mouse retina and communicate calcium waves to regulate blood flow, mediating a critical role in neurovascular coupling *in vivo* (Alarcon-Martinez et al., 2020) (Fig. 3 D). These pericyte-to-pericyte TNTs are disrupted by elevated intraocular pressure in a mouse model of glaucoma, which induces calcium

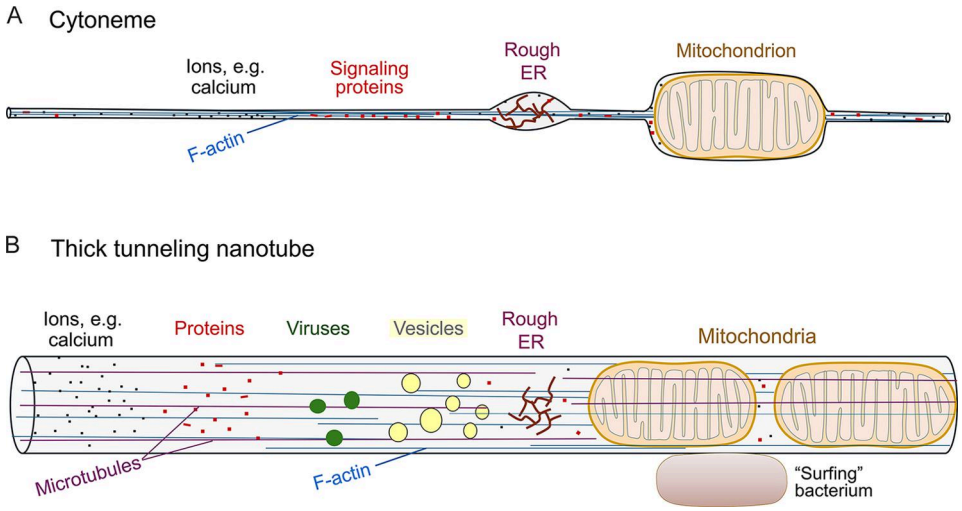

Figure 2. **Schematic diagram depicting the contents of a cytoneme and a thick TNT. (A)** Cytonemes contain a core of F-actin filaments with various ions, including calcium fluxes and signaling molecules such as WNT proteins; however, some can also contain mitochondria and rough ER in bulges. **(B)** The contents of thick TNTs always include long structural F-actin filaments, but they can also contain microtubules and multiple other cytoplasmic components. Contents can include not only ions and signaling molecules and/or other proteins (normal or pathogenic), as well as viruses, vesicles of various types and sizes, rough ER, and mitochondria; in addition, some bacteria can "surf" along the surface of TNTs. The contents are drawn roughly to scale.

influx-mediated neuronal damage in the retina (Alarcon-Martinez et al., 2022). Long TNTs interconnecting pericytes have also recently been characterized in the macula of human eyes (Hein et al., 2024).

TNTs can also interconnect pericytes in the retina with endothelial cells, and *in vitro* treatment of pericytes with PDGF can induce such TNTs (Fig. 3 D). These TNTs transport mitochondria unidirectionally from pericytes to endothelial cells. In a metabolic rescue process, this mechanism restored a functional mitochondrial network after experimental depletion of endothelial cell mitochondria (Kempf et al., 2024).

Another TNT-mediated mitochondrial rescue process has been reported involving a transfer from stem cells to adipose tissue macrophages to alleviate a mouse model of pregnancy-induced diabetes (Chen et al., 2025a). Similarly, TNT-mediated transfer of mitochondria has been reported to contribute to therapeutic angiogenesis in a mouse model of hindlimb ischemia (Che et al., 2025b). In a model of cardiac sepsis, cardiomyocytes form TNTs with neighboring cells such as endothelial cells and fibroblasts to transfer damaged mitochondria to these neighboring cells, which can help the cardiomyocytes but contributes to sepsis-induced cardiac damage (Song et al., 2026). Consequently, the use of TNTs to interconnect cells with neighbors or with other cell types appears to be widespread in both embryonic and adult organisms.

Within the brain, TNTs can interconnect neuronal and microglial cells to permit exchanges of mitochondria and α-synuclein (Chakraborty et al., 2023). TNTs also contribute to the generation of a network of interconnected neurons (Khattar et al., 2022; Palese et al., 2025; Rakotobe and Zurzolo, 2025). Short TNT-like structures extending outward from neuronal dendrites provide interconnections termed dendritic nanotubes. Dendritic nanotubes in the visual cortex (shown to be different from synaptic connections) provide pathways for not only calcium signaling but also for transporting Alzheimer's disease human β-amyloid in mouse brains. This dendritic nanotube network is altered in a mouse model of early Alzheimer's disease prior to amyloid plaque formation, suggesting a role in the progression of Alzheimer's pathology (Chang et al., 2025). In fact, TNTs have also been implicated in the spread of prion, Parkinson's, and Huntington disease proteins in the central nervous system (Victoria and Zurzolo, 2017). Not surprisingly, there are also multiple examples of roles for TNTs in the initial cell-to-cell spread of pathogenic viruses including HIV, influenza virus, herpesvirus, SARS-CoV-2, and others (Jansens et al., 2020; Lv et al., 2024; Pepe et al., 2022; Sowinski et al., 2008; Weir et al., 2025), as well as even nanoplastic particles (Chang and Wang, 2025).

Cancer–cancer cell interconnections

TNTs/tumor microtubes can interconnect cancer cells (Fig. 3 E) and have been identified in a wide range of cancers (Table S2). They have been studied most extensively in glioma brain cancers but also in many other blood and solid cancers, including other brain, head-and-neck, lung, colon, breast, ovarian, and prostate cancers, as well as leukemias (Cervantes and Zurzolo, 2021; Chen and Zhao, 2024; Osswald et al., 2015; Pinto et al., 2021; Sáenz-de-Santa-María et al., 2017; Venkataramani et al., 2022). TNTs are thought to play important roles in promoting cancer progression or in the protection of tumor cells against stressors, including hypoxia and metabolic stress (Desir et al., 2016; Kretschmer et al., 2019). They can contribute to cancer promotion, protection from cancer chemotherapy and radiation therapy, and maintenance of tumor fitness in the face of hypoxic and chemical stresses. For example, TNTs have been implicated in the development of resistance to chemotherapy in a variety of cancers (Desir et al., 2018; Sarkari and Lou, 2024). Mechanistically,

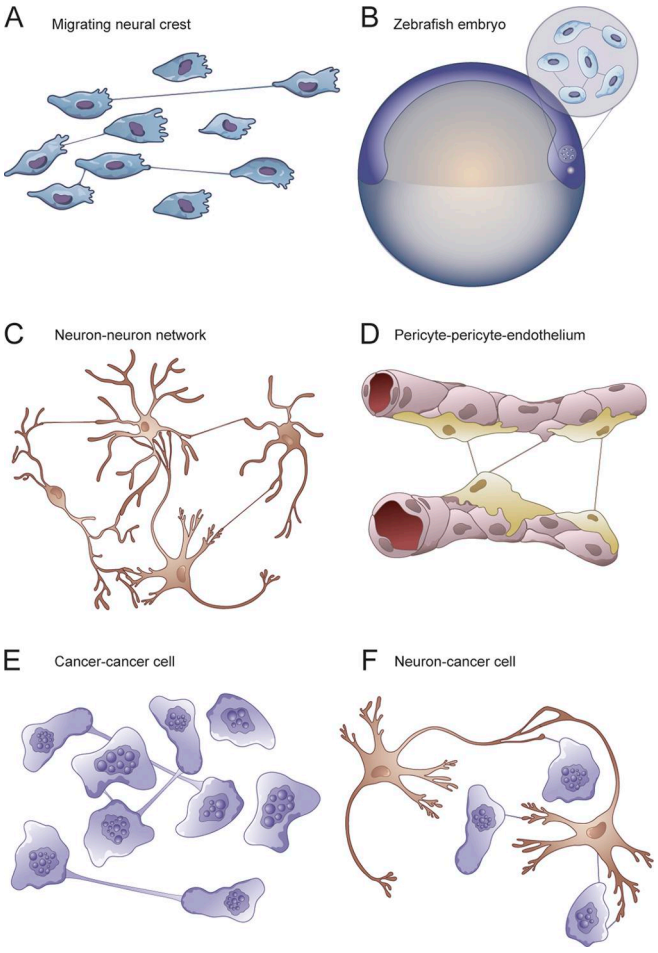

Figure 3. **TNTs can interconnect embryonic, adult, and/or malignant cells.** These diagrams depict examples of the wide variety of cells known to become interconnected by TNTs or TNT-like structures. **(A)** Embryonic neural crest cells can be interconnected by long, thin TNT-like structures as they migrate during development. **(B)** During zebrafish gastrulation, the migrating embryonic cells have TNTs that link cells to other cells. **(C)** Neurons in the brain have TNT-mediated intercellular connections that form an interconnected network. **(D)** Pericytes can use TNTs to connect to other pericytes or even to endothelial cells in adjacent capillaries. **(E)** A wide variety of human cancer cell types display prominent linkages with other cancer cells via TNT-like structures also termed tumor microtubes. **(F)** Neurons can form TNT-mediated connections to malignant cells to promote tumor progression and protect against external stresses including hypoxia and chemotherapy.

tumor cells suffering from a high concentration of a chemotherapeutic agent are suggested to be able to reduce toxic levels by efflux to other interconnected cells having lower levels of the agent. Alternatively, TNTs can mediate the sharing of the multidrug resistance membrane protein P-glycoprotein (MDR1) with other interconnected cancer cells (Pasquier et al., 2012).

In human and mouse *in vivo* tissues, malignant glioma cells interconnected by TNT-like tumor microtubes were found to differ from non-interconnected cells by the elevated expression of stem cell markers, especially nestin along with Musashi and Sox2; they also showed higher levels of the proliferation marker Ki67, all consistent with cancer promotion (Xie et al., 2021). Cancer cells that had been integrated into this TNT-mediated network displayed enhanced resistance to radiation therapy (Xie et al., 2021). In addition, TNTs are thought to contribute to the general distribution-redistribution of vesicles, including lysosomes and autophagosomes, between cancer cells, as well as mitochondria in tumors (Fig. 4), which could enhance overall tumor metabolism and fitness (Libring et al., 2024; Sáenz-de-Santa-María et al., 2017; Zampieri et al., 2021). For example, pheochromocytoma PC12 cells that would otherwise undergo apoptosis after UV treatment can be rescued by the transfer of fresh mitochondria via TNTs from untreated cells (Wang and Gerdes, 2015).

In an alternative mechanism, the formation of TNTs between glioblastoma cells and adjacent nonmalignant astrocytes could modify their tumor microenvironment. TNT-mediated transfer of tumor cell–modified mitochondria to neighboring astrocytes is suggested to promote a more tumor-supportive local environment with altered astrocyte glutamine metabolism and resistance to hypoxia (Valdebenito et al., 2021). Conversely, malignant multiple myeloma cells can use TNTs to hijack mitochondria from adjacent nonmalignant bone marrow stromal cells to promote their own bioenergetic plasticity and fitness (Marlein et al., 2019). Besides mitochondria, other cellular components such as vesicles are known to be redistributed, and even cancer-promoting mutated oncogenes such as oncogenic *KRAS* can be shared between interconnected cancer cells (Desir et al., 2019). Similarly, the microRNA miR-115 that promotes cell proliferation and invasion can also be transferred between bladder cancer cells via TNTs (Lu et al., 2019). Conceptually, TNTs can enhance tumor progression by: (1) sharing mitochondria with other cancer cells to enhance overall metabolic fitness, (2) helping to protect against stressors resulting from chemotherapy, radiotherapy, and hypoxia, and (3) spreading oncogenic factors. Yet another variation on the theme of molecular sharing to enhance tumor aggressiveness is the ability of breast cancer cells to "borrow" a metastasis-promoting protein from adjacent mesenchymal stromal cells to enhance tumor dissemination (Sinha et al., 2024).

Cancer-host lymphocyte, macrophage, and stem cell interconnections

As reviewed elsewhere, TNTs interconnect multiple different types of immune cells, playing roles in their differentiation and subsequent overall immune surveillance (Cervantes and Zurzolo, 2021; Watkins and Salter, 2005; Zhu et al., 2021). TNTs also play roles in cancer immunosurveillance; for example, TNTs can promote long-distance linkage between natural killer (NK) cells and target cells, and physically disrupting TNTs reduces the lysis of targeted tumor cells (Chauveau et al., 2010). Particularly intriguing recent findings have focused on the roles of TNT-mediated transfer of mitochondria between normal, malignant, or immune cells to enhance or cripple immune cell function and/or support tumor cell metabolism (Fig. 4). TNTs can be used by T cells to obtain fresh mitochondria from bone marrow stem cells, thus enhancing their supply of mitochondria and overall metabolic fitness and T cell efficiency (Baldwin et al., 2024). Analogously, various cancer cells can hijack immune cell mitochondria from T or NK cells to both enhance cancer cell metabolism and

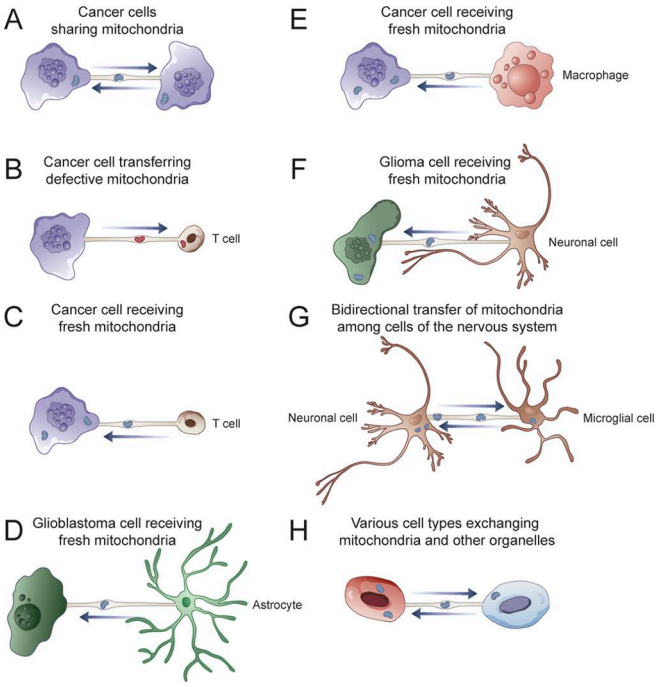

Figure 4. **Mitochondrial transfer between multiple cell types mediated by TNTs.** Increasing numbers of cell types have been reported to participate in TNT-mediated cell-to-cell transfer of mitochondria. **(A)** Tumor cells can share mitochondria with each other via TNTs for mutual support, e.g., (Lou et al., 2012b). **(B)** Cancer cells can use TNTs to transfer genetically defective mitochondria to cripple tumor-infiltrating T lymphocytes for immune evasion (Ikeda et al., 2025). **(C)** Tumor cells can also steal healthy mitochondria from T cells via TNTs to support their metabolism while also depleting the immune cells (Saha et al., 2022). **(D)** Malignant glioblastoma cells can hijack mitochondria from astrocytes using TNTs to enhance their tumorigenicity (Watson et al., 2023). **(E)** Macrophages can provide more mitochondria to cancer cells to enhance their invasiveness both *in vitro* and *in vivo* (Hanna et al., 2019). **(F)** Neurons can transfer mitochondria to cancer cells via TNT-like structures to support tumor cell metabolism, stemness, resistance to stressors, and metastasis (Hoover et al., 2025). **(G)** Microglial cells can transfer mitochondria to neuronal cells afflicted by α-synuclein as a potential rescue mechanism (Chakraborty et al., 2023). **(H)** More and more examples of TNT-mediated mitochondrial transfer are being reported, suggesting that this process may be common not only in disease states, but also potentially in normal tissue biology, e.g., (Kempf et al., 2024)—a possibility to be clarified in the future.

impair immune cell function, both *in vitro* and *in vivo* (Saha et al., 2022). Conversely, cancer cells can transfer faulty mitochondria to T cells to blunt immune killing (Ikeda et al., 2025; Liang et al., 2025). Consequently, the transfer of mitochondria through TNTs can enhance both immune and malignant cell metabolism, deplete immune cell mitochondria, or even transfer faulty mitochondria from tumor cells to cripple immune cells.

Tumor cells can interact with host macrophages using potentially bidirectional TNT-inductive mechanisms. Conditioned media from macrophages containing epidermal growth factor (EGF) can induce TNTs in various human cancer cell lines. Depletion of the TNT-promoting protein M-Sec (also known as the TNF-α–induced protein TNFAIP2, repeatedly associated with TNT induction) resulted in inhibition of 3D *in vitro* tumor cell invasion (Carter et al., 2019). Conversely, nonmalignant macrophages can generate TNTs in a process involving Cdc42 and Rac1 (Hanna et al., 2017). Interestingly, TNTs linking tumor cells and macrophages can promote tumor cell invasion in an *in vivo* zebrafish model system of metastatic invasion stimulated by EGF and dependent on M-Sec (Hanna et al., 2019). A novel, intriguing physical mechanism promoting extravasation was found to be based on long, thin, membranous TNT-like structures that provide physical links extending from macrophages to tumor cells on the other side of endothelia; the TNTs were apparently from both macrophages and tumor cells (Genna et al., 2023). These macrophage-mediated TNT-like structures spanning the endothelium can reportedly assist tumor cell translocation through the endothelial cell barrier during extravasation for seeding of metastases. In fact, mice deficient in M-Sec, including in their macrophages, showed reduced experimental metastasis (Genna et al., 2023). If these TNT-like structures linking tumor cells within blood vessels lined with a basement membrane to host macrophages on the other side of endothelia were to possess active contractility, we speculate that the tumor cell could be pulled physically through the endothelial barrier. In fact, long prehensile cell protrusions of tumor cells previously shown to be contractile for pulling cells through basement membrane barriers (Nazari et al., 2023) might be precursors of TNT-like structures that would contract to help pull tumor cells into tissues during extravasation—a testable speculative hypothesis.

Neuronal-cancer interconnections and interactions

Increasing data indicate the nervous system can make substantial contributions to tumorigenesis, the cancer immune environment, and even metastasis of a wide variety of cancer types, including lung, breast, and colorectal cancers (Huang et al., 2025; Magnon and Hondermarck, 2023). Although neuronal-cancer cell input can occur via synaptic connections (Sakthivelu et al., 2025; Savchuk et al., 2025), neuronal cell-to-cancer cell TNTs or TNT-like interconnecting structures have also been documented (Hoover et al., 2025) (Fig. 3 F). Such TNT-like connections can provide fresh mitochondria to cancer cells to promote more effective cancer cell function (Hoover et al., 2025). Approximately 30% of breast cancer cells showed such transfers *in vitro*, and disruption of TNTs with cytochalasin inhibited the transfer, though more specific inhibitory methods were not tested. Besides neuronal cells, primary fibroblasts and a pre-adipocyte cell line could also transfer mitochondria to recipient cancer cells *in vitro*. Interestingly, *in vivo* xenograft analyses revealed enrichment in metastases: starting from a low 5% initial proportion of cells displaying a genetic mitochondrial transfer marker in the primary tumor, the percentage rose dramatically to a quarter of total cancer cells in brain metastases and to nearly half in lung metastases (Hoover et al., 2025). These findings were partially confirmed using a melanoma cancer cell model. Human breast cancer metastases also showed increased mitochondrial loads after pathological analysis. Taken together, these findings support a key role for TNTs and mitochondrial transfer from neuronal and possibly other cell types to promote cancer metastasis (Hoover et al., 2025).

Box 2. **Reported molecular mediators of TNT/tumor microtube formation and maintenance.**
The categorizations of candidates listed below are provisional and will need further mechanistic exploration. Recent papers are often cited preferentially here to provide bibliographic access to the previous literature.

Candidate inducers

M-Sec (TNFAIP2) (Barutta et al., 2021; Che et al., 2025a; Fu and Yuan, 2024; Hase et al., 2009; Wang et al., 2025a)
- Connexin 43 (Tishchenko et al., 2020; Zhang et al., 2003)
- Gap-43 (Osswald et al., 2015)
- TTyh1 (Jung et al., 2017)
- HGF (Awanis et al., 2023)
- TGF-β (Joseph et al., 2022)
- EGF (Carter et al., 2019)
- PDGF (Kempf et al., 2024)
- WNT and calmodulin-dependent protein kinase II (CaMKII) (Vargas et al., 2019)

Candidate elongation mediators

Cdc42 (Dash et al., 2021; Hanna et al., 2017)
- Rac1 (Dash et al., 2021; Hanna et al., 2017)
- Arp2/3 (Dash et al., 2021; Hanna et al., 2017) but see (Henderson et al., 2023; Raghavan et al., 2024)
- Cofilin (Chen et al., 2025b)
- Eps8 (Henderson et al., 2023; Kretschmer et al., 2019)
- IRSp53/I-BAR domain (Henderson et al., 2023; Madarasz et al., 2023)
- Rab8 (Burtey et al., 2015; Zhu et al., 2018)
- Rab11 (Zhu et al., 2018)

Candidate structural proteins/mediators

F-actin Rustom et al. (2004)
- Microtubules (Önfelt et al., 2006)
- Myosin X (Gousset et al., 2013)

Other candidates

Interferon-α (Omsland et al., 2020)
- RAS superfamily (Dash et al., 2021)
- MAP kinase (Cole et al., 2021)
- FAK and NNP-2 (Saénz-de-Santa-María et al., 2017)
- PI 3-kinase (Kretschmer et al., 2019)
- mTOR (Desir et al., 2016)
- RalGPS2 via Akt and PDK1 (D'Aloia et al., 2021)
- Myosin V (Chang et al., 2022)
- Nucleolin (Dagar et al., 2021b)
- Ral (Hase et al., 2009)
- Exocyst protein Sec3 (Dash et al., 2021)
- N-cadherin (Chang et al., 2022)
- Tetraspanins CD9 and CD81 (Notario Manzano et al., 2024)
- CD38 (Marlein et al., 2019)
- Thrombospondin (Joseph et al., 2022)
- Syncytin (Zhang and Schekman, 2023)
- Rhes (Sharma and Subramaniam, 2019)
- LST1 (Raghunathan et al., 2001; Schiller et al., 2013)
- Chaperone Erp29 (Pergu et al., 2019)
- p53 activation (Wang et al., 2011 but see Andresen et al., 2013)
- NS1 protein of Zika virus (Michita et al., 2025)
- Matrix environment (e.g., alignment) (Jana et al., 2022)
- Rho kinase (ROCK) inhibition (da Silva et al., 2019)
- mDia inhibition (Becker et al., 2022)

Molecules implicated in TNT formation, maintenance, and function

Two noteworthy features of the literature on TNT formation and maintenance are the wide variety of molecules implicated in TNT formation and the conceptual difficulty in identifying the molecules needed for induction of TNTs versus their maintenance. As for other complex biological processes, multiple cellular molecules could be required for TNT maintenance, making it difficult to determine which molecule(s) are essential for their initial formation. Box 2 provides a partial listing of molecules implicated in the formation or maintenance of TNTs and related structures. Many of the molecules implicated to date appear to differ between cytonemes and TNTs, but it is not clear whether this distinction is definitive, especially considering the striking heterogeneity of the reported molecular drivers of TNTs in different publications and the capacity of both TNTs and cytonemes to carry mitochondria and rough ER.

Plausible candidates for inducers of TNTs in Box 2 include growth factors such as EGF and HGF, but each is well-known to stimulate multiple other cellular processes—that is, they can stimulate TNT formation, but as signaling molecules they may not be the direct molecular initiators/mediators of TNT

formation. At an intracellular mechanistic level, a logical driver for generating thin cellular protrusions would be the Rho GTPase Cdc42, which is well-known to induce filopodia (Nobes and Hall, 1995). Actin polymerization is required, since the core of TNTs includes F-actin, and the actin remodeling protein cofilin has been implicated in TNTs (Chen et al., 2025b; Dagar et al., 2021b). Another plausible candidate, Arp2/3, was implicated in TNT formation in macrophage RAW cells (Hanna et al., 2017), but not in neuronal CAD cells, where inhibition of its activity in promoting F-actin branching instead drove the formation of longer filopodial precursors of TNTs via unbranched linear F-actin filaments (Henderson et al., 2023). Whether these differences reflect cell type specificity or differing roles in actin regulation remains to be determined. What is even less clear is which specific molecular drivers are involved in generating the unusual lengths of the tubular cell extensions characteristic of both TNTs and cytonemes compared with filopodia.

A particularly attractive molecular mechanism for TNT induction involves the regulatory protein M-Sec (TNFAIP2), which, when overexpressed, can promote the formation of long cellular protrusions and TNTs; M-Sec has also been implicated in TNT formation in multiple cancers (Che et al., 2025a; Fu and Yuan, 2024; Hase et al., 2009). M-Sec supports TNT elongation by translocating to the plasma membrane with the help of nucleolin and interacting with Ral, LST1, cofilin and finally the exocyst complex for stimulation of actin filaments and insertion of the plasma membrane needed for the TNT (Dagar et al., 2021b; Raghunathan et al., 2001; Schiller et al., 2013). However, how universal this plausible sequence may be for other cell types remains to be clarified, as well as the exact sequential molecular steps and mechanisms—ideally established by future *in vitro* reconstitution experiments.

A recent microscopy study has identified an additional biophysical mechanism for TNT formation based on filopodia: a filopodium from 1 cell reaches out and adheres to a filopodium from another cell using N-cadherin. One of the filopodia then retracts with the help of a helical twist in the filopodial shaft facilitated by myosin V, resulting in a single long TNT linking the 2 cells. In this study, most TNTs were closed-ended, leaving unanswered how the open-ended TNTs that can transport mitochondria between cells are generated (Chang et al., 2022).

What mechanisms/motor proteins mediate the cell-to-cell translocation of organelles such as mitochondria, and how is directionality of transfer determined? Candidates include the microtubule motor protein kinesin KIF5B and contractile protein myosin VI, but not the myosin II molecule implicated in many other cellular contractile processes (Halasz et al., 2024), and possibly myosin XIX (Qin et al., 2021). A key regulator of mitochondrial translocation is Miro1, which is a Rho GTPase on mitochondria that regulates mitochondrial transfer along TNTs (Nahacka et al., 2022). The processes of active transport of organelles within TNTs can be mimicked and reversed experimentally (Gong et al., 2025). External manipulation of TNT cargoes may ultimately be able to determine more definitively the endogenous biophysical forces and motor mechanisms used to transport organelle cargo, including mitochondria.

General conclusions

- TNTs, cytonemes, and their morphological relatives mediate distant cell–cell interconnections; they can be up to hundreds of micrometers long and have a wide range of diameters, ranging from slender cytonemes to thick TNTs and TNT-like structures.
- They can be initiated and maintained by a wide range of molecules, and a current dilemma is that neither cytonemes nor TNTs have a specific molecular marker.
- The intercellular communication systems based on cytonemes and TNTs are needed for normal embryonic development and perhaps adult tissue homeostasis.
- TNT-mediated communication becomes hijacked in diseases that include cancer and neurological diseases.
- Cancer cells use TNT communication and organelle exchange systems to support cancer progression and to defend against a variety of attacking stressors, e.g., hypoxia, host immune defenses, chemotherapeutic agents, and other stressors

Remaining questions and future opportunities

Many challenging questions and research opportunities remain as this field continues to expand rapidly.

A spectrum or a heterogeneous population of structures?

Although long filopodia, cytonemes, TNTs, TNT-like structures, and tumor microtubes might comprise a spectrum of tubular structures, distinctive features of each exist as indicated in Box 1 and Fig. 1, making it important to answer this question more definitively. For example, although cytonemes are classically considered to be closed-ended signaling conduits, TNTs can either be open-ended or closed-ended due to a gap junction, thereby blocking their function in organelle transport. But can TNTs ever be interconverted from closed- to open-ended? A technical problem is that many studies of each type of TNT or TNT-like structure have used a different cell or tissue system. One approach might be to find cell types that can make > 1 class of these structures, and then to characterize the molecular and morphological features that are shared between these TNTs versus those that are distinct, as well as whether interconversion is possible, for example, as documented by live-cell imaging.

Molecular mechanisms of TNT formation?

A major challenge will be to establish exactly how TNTs are generated, ideally by using *in vitro* reconstitution approaches, such as those used to establish the pathways of protein secretion. The partial list of candidate molecules in Box 2 will need further classification into shared and cell type–specific molecules, as well as their mechanistic pathways.

Necessary vs. sufficient mechanisms?

It will be important to determine in the future which of the molecules listed in Box 2 are necessary as opposed to being able to initiate TMT formation. Although M-Sec/TNFAIP2 and a couple of other molecules have been examined for sufficiency by overexpression analysis, the latter type of approach will be

valuable for all the other candidates with testing in multiple different cell types. Another caveat is that some growth factors such as HGF may trigger permissive cells to form TNTs, but the signaling and downstream mechanistic pathways may differ.

Which regulatory systems govern TNT diameters, cargo transport, and other functions of different TNTs?

Although different TNTs and tumor microtubes can have substantially different diameters, a potential source of confusion is that TNTs that appear to be thick by confocal microscopy can in fact be comprised of a bundle of thin individual TNTs as clarified by careful ultrastructural analyses (Sartori-Rupp et al., 2019). Answering how diameters are regulated will therefore first require ultrastructural evidence that putative thick TNTs are authentic single tubular structures, followed by comparisons of mechanisms between different cell types. Also needing elucidation is how the choice of which types of cargo are transported is made, then identifying the motor mechanisms that transport mitochondria or other organelles, including how the directionality of transfer is determined. The processes of active transport of organelles within TNTs can be mimicked and reversed experimentally (Gong et al., 2025). External manipulation of TNT cargoes may help determine the endogenous cellular forces involved to facilitate characterization of the motor mechanisms used to transport organelle cargo such as mitochondria.

Generalizable?

Although many molecules have been implicated in TNT formation or maintenance, and some in sufficiency, the studies are often based on only a single cell type. It will eventually be important to determine which of the putative initiators and those involved in elongation versus stabilization of TNTs are general for other cell types. It may be quite possible for these nanotubular structures to be regulated in different ways in different types of cells—an important point to establish definitively.

One overall possibility is that TNTs, cytonemes, and tumor microtubes are cell type specific (Cervantes and Zurzolo, 2021). It may help to consider an analogy with another complex field in cell biology, that of the modes and mechanisms of 3D cell migration. In that field, there turned out to be clearly distinct functional mechanisms depending on cell type, experimental condition, and microenvironment, and yet there were also frequently shared molecular mediators (Yamada and Sixt, 2019). Whether identifying this pattern of differences and overlaps of mechanisms will also be the case for TNT research will likely challenge the cytoneme and TNT fields for many years to come. One type of approach, though painful, would be to test each of the reported regulators of TNTs in each biological system, ideally within the same laboratory. For example, the reported requirements for Arp2/3 or p53 activation in TNT formation differ depending upon the cell type being examined (Andresen et al., 2013; Wang et al., 2011), possibly due to their multiple cell biological roles. This type of discrepancy contributing to the so-called "reproducibility crisis" could be alleviated by systematic tests of generalizability to separate out cell-specific mechanisms from more broadly shared molecular mechanisms.

In vitro but also *in vivo*?

Although the widespread use of *in vitro* culture and co-culture of various cell types has provided a powerful tool for establishing concepts of what TNTs and tumor microtubes can do, what these cells actually do in vivo is not as definitive. Although dynamics of tumor microtubes have been successfully imaged by two-photon microscopy *in vivo* for many days (Osswald et al., 2015), in-depth real-time imaging to characterize vesicle and mitochondrial transfers *in vivo* has been impeded by technical imaging limitations. Instead, some papers have used markers to provide quantitative evidence, for example, that mitochondrial transfer has occurred—the caveat is that some alternative or additive mechanism besides TNT transfer might have been involved *in vivo*. In fact, use of the mitochondrial marker MitoTracker to show cell-to-cell transfer has been challenged due to its capacity to transfer between cells independently of cell–cell contact, making the use of genetic markers important (Hole et al., 2026). As technology advances, a future opportunity will be to show directly by intravital imaging the existence, extent (rare or widespread), and mechanisms of TNT-mediated transfers of specific organelles such as mitochondria *in vivo*.

A related question involves determining how widespread the roles of cytonemes and TNTs are in the development and homeostasis of all tissues. It is conceivable, but not established, that cytoneme and TNT-mediated interconnections are widespread in both embryos and adult organisms; but until reliable markers can be identified, this question will remain open. In the meantime, application of automated machine-learning algorithms may help detect TNTs in microscopy images (Ceran et al., 2022), as could lattice light sheet imaging (Parker et al., 2017) and super-resolution radial fluctuation microscopy (Hoover et al., 2025).

Are some TNTs contractile?

Although TNT-like long filopodia linking embryonic vertebrate lens and retinal epithelia appear to be contractile (Chauhan et al., 2009), the possibility of TNT contractility needs further rigorous experimental evaluation. In addition, whether the long contractile cell protrusions that can contract to remodel collagen (Nazari et al., 2023) might be precursors of contractile TNTs/tumor microtubes will also need stringent testing. If TNT contractility can be established, we speculate that tumor cells reported to link to host cells such as macrophages on the other side of the endothelial barrier (Genna et al., 2023) might use TNT-like contractile structures for pulling cancer cells across endothelia during tumor cell extravasation. An additional speculative possibility is that TNT-facilitated crossing of the endothelium and its basement membrane might also be used by normal immune cells to enter and leave tissues.

How do TNTs connect to target cells?

A TNT that extends out to contact another cell must undergo membrane fusion with the target cell to open an intercellular conduit for transport. How that fusion occurs will need to be determined, e.g., possibly via some unknown targeting mechanism and a fusogen to create a fusion pore (Rakotobe and Zurzolo, 2025).

Can TNTs ever be therapeutic targets?

Considered from a clinical standpoint, disruption of TNT functions could potentially block TNT-mediated cancer cell defenses against chemotherapeutic agents and radiation therapy, mitochondrial defense mechanisms, and other TNT protective strategies. Proposed approaches have included inhibiting gap junctions, neuronal signaling, and even Wnt signaling (Beichert et al., 2025; Chen and Zhao, 2024; Feng et al., 2025). A major concern, however, is that in analogy to classical antiproliferation chemotherapy approaches, targeting molecules and pathways necessary for not only TNTs but also other critical cellular functions will result in too many clinical side effects. Combining anti-TNT treatments with other modalities in combination could alleviate this problem. For example, inhibiting tumor microtubes by modulating protein kinase C can be combined with therapeutic radiation for anti-glioblastoma tumor therapy (Azorin et al., 2026).

An interesting alternative approach might be to turn their TNTs against cancer cell networks, i.e., using them to spread "nanomedicines" throughout the cancer cell system. For example, anticancer nanoparticles with shapes optimized for TNT-mediated transfer or with piezoelectric properties might spread quickly through TNT networks to kill cancer cells that would otherwise be difficult to reach by diffusion alone (Liu et al., 2025; Ottonelli et al., 2022; Sierri et al., 2025). Similarly, liposomes that could contain chemotherapeutic agents can also be distributed through TNTs (Formicola et al., 2019). A major challenge is how therapeutic liposomes or nanoparticles can be targeted to disrupt TNTs yet not disrupt other cellular processes. It will also be necessary to obtain robust and selective uptake: although cancer cells are known to ingest some nanoparticles and liposomes, particularly if targeted to a particular cancer marker, the magnitude of uptake and avoiding subsequent damage to non-cancerous cells will be concerns. It would be ideal if specific TNT or cancer microtube molecular targets can be identified, ideally some targetable cell surface marker to permit the use of antibody-toxin chimeras.

A physical approach to disrupting TNTs using low-intensity alternating electric fields could disrupt TNTs in malignant mesothelioma cells with altered biomarkers *in vivo*, though whether the effects were due solely to TNT disruption was not clear (Sarkari et al., 2023). These examples again point to the need for innovative approaches to alter TNT functions selectively in tumors without disrupting essential normal cell–cell interactions. On the other hand, because some particular cancers can be treated by a nonspecific treatment such as antimitotic chemotherapy, targeting TNTs in particularly susceptible cells might eventually become practical therapeutically in selected cancers, infections, or neurological diseases.

In summary, the fields of TNT and cytoneme research have expanded rapidly from pioneering studies on their roles in cancer cell self-protection and in signaling during embryonic development to discoveries of a remarkable range of cell–cell communication and organelle-sharing mechanisms. The growing numbers of tissues and diseases, including cancers, that use these nanotubular structures for a wide range of functions, combined with the multiple still-unanswered questions in this field, predict an exciting future for this increasingly important area of cell biological research.

Online supplemental material

Table S1 summarizes examples of developmental systems in which cytonemes have been characterized, and Table S2 lists examples of tunneling nanotubes (also termed cancer microtubes) in various cancers.

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References

Alarcon-Martinez, L., Y. Shiga, D. Villafranca-Baughman, N. Belforte, H. Quintero, F. Dotigny, J.L. Cueva Vargas, and A. Di Polo. 2022. Pericyte dysfunction and loss of interpericyte tunneling nanotubes promote neurovascular deficits in glaucoma. *Proc. Natl. Acad. Sci. USA*. 119: e2110329119. https://doi.org/10.1073/pnas.2110329119

Alarcon-Martinez, L., D. Villafranca-Baughman, H. Quintero, J.B. Kacerovsky, F. Dotigny, K.K. Murai, A. Prat, P. Drapeau, and A. Di Polo. 2020. Interpericyte tunnelling nanotubes regulate neurovascular coupling. *Nature*. 585:91–95. https://doi.org/10.1038/s41586-020-2589-x

Alberts, B., R. Heald, A. Johnson, D. Morgan, M. Raff, K. Roberts, and P. Walter. 2022. Molecular Biology of the Cell. W. W. Norton & Company, New York, NY. 5069.

Andresen, V., X. Wang, S. Ghimire, M. Omsland, B.T. Gjertsen, and H.H. Gerdes. 2013. Tunneling nanotube (TNT) formation is independent of p53 expression. *Cell Death Differ*. 20:1124. https://doi.org/10.1038/cdd.2013.61

Antanaviciute, I., K. Rysevaite, V. Liutkevicius, A. Marandykina, L. Rimkute, R. Sveikatiene, V. Uloza, and V.A. Skeberdis. 2014. Long-distance communication between laryngeal carcinoma cells. *PLoS One*. 9:e99196. https://doi.org/10.1371/journal.pone.0099196

Awanis, G., S. Banerjee, R. Johnson, S. Raveenthiraraj, A. Elmeligy, D. Warren, J. Gavrilovic, and A. Sobolewski. 2023. HGF/c-Met/β1-integrin signalling axis induces tunneling nanotubes in A549 lung adenocarcinoma cells. *Life Sci. Alliance*. 6:e202301953. https://doi.org/10.26508/lsa.202301953

Azorin, D.D., D.C. Hoffmann, N.R. Hebach, E. Jung, D. Hausmann, M. Ratliff, L. Hai, S. Horschitz, A. Jabali, M. Osswald, et al. 2026. Screening for tumor microtube-targeting drugs identifies PKC modulators as multipotent inhibitors of glioblastoma progression. *Cancer Discov*. 16:367–390. https://doi.org/10.1158/2159-8290.CD-24-0414

Baldwin, J.G., C. Heuser-Loy, T. Saha, R.C. Schelker, D. Slavkovic-Lukic, N. Strieder, I. Hernandez-Lopez, N. Rana, M. Barden, F. Mastrogiovanni, et al. 2024. Intercellular nanotube-mediated mitochondrial transfer enhances T cell metabolic fitness and antitumor efficacy. *Cell*. 187: 6614–6630.e21. https://doi.org/10.1016/j.cell.2024.08.029

Barutta, F., S. Kimura, K. Hase, S. Bellini, B. Corbetta, A. Corbelli, F. Fiordaliso, A. Barreca, M. Papotti, G. Ghiggeri, et al. 2021. Protective role of the M-Sec–Tunneling nanotube system in podocytes. *J. Am. Soc. Nephrol.* 32: 1114–1130. https://doi.org/10.1681/ASN.2020071076

Becker, K.N., K.M. Pettee, A. Sugrue, K.A. Reinard, J.L. Schroeder, and K.M. Eisenmann. 2022. The cytoskeleton effectors Rho-Kinase (ROCK) and mammalian diaphanous-related (mDia) formin have dynamic roles in tumor microtube formation in invasive Glioblastoma cells. *Cells*. 11:1559. https://doi.org/10.3390/cells11091559

Beichert, J., D.C. Hoffmann, F. Winkler, and M. Ratliff. 2025. Innovative therapeutic strategies targeting the network architecture of glioblastoma. *Clin. Cancer Res.* 31:2864–2871. https://doi.org/10.1158/1078-0432.CCR-25-0018

Bischoff, M., A.C. Gradilla, I. Seijo, G. Andrés, C. Rodriguez-Navas, L. Gonzalez-Mendez, and I. Guerrero. 2013. Cytonemes are required for the establishment of a normal Hedgehog morphogen gradient in *Drosophila* epithelia. *Nat. Cell Biol.* 15:1269–1281. https://doi.org/10.1038/ncb2856

Brunt, L., G. Greicius, S. Rogers, B.D. Evans, D.M. Virshup, K.C.A. Wedgwood, and S. Scholpp. 2021. Vangl2 promotes the formation of long cytonemes to enable distant Wnt/beta-catenin signaling. *Nat. Commun.* 12:2058. https://doi.org/10.1038/s41467-021-22393-9

Burtey, A., M. Wagner, E. Hodneland, K.O. Skaftnesmo, J. Schoelermann, I.R. Mondragon, H. Espedal, A. Golebiewska, S.P. Niclou, R. Bjerkvig, et al. 2015. Intercellular transfer of transferrin receptor by a contact-Rab8-dependent mechanism involving tunneling nanotubes. *FASEB J.* 29: 4695–4712. https://doi.org/10.1096/fj.14-268615

Carter, K.P., S.J. Hanna, A. Genna, D. Lewis, J.E. Segall, and D. Cox. 2019. Macrophages enhance 3D invasion in a breast cancer cell line by induction of tumor cell tunneling nanotubes. *Cancer Rep.* 2:e1213. https://doi.org/10.1002/cnr2.1213

Ceran, Y., H. Ergüder, K. Ladner, S. Korenfeld, K. Deniz, S. Padmanabhan, P. Wong, M. Baday, T. Pengo, E. Lou, and C.B. Patel. 2022. TNTdetect.AI: A deep learning model for automated detection and counting of tunneling nanotubes in microscopy images. *Cancers (Basel)*. 14:4958. https://doi.org/10.3390/cancers14194958

Cervantes, D.C., and C. Zurzolo. 2021. Peering into tunneling nanotubes-The path forward. *EMBO J.* 40:EMBJ2020105789. https://doi.org/10.15252/embj.2020105789

Chakraborty, R., T. Nonaka, M. Hasegawa, and C. Zurzolo. 2023. Tunnelling nanotubes between neuronal and microglial cells allow bi-directional transfer of alpha-Synuclein and mitochondria. *Cell Death Dis.* 14:329. https://doi.org/10.1038/s41419-023-05835-8

Chang, M., S. Krüssel, L.K. Parajuli, J. Kim, D. Lee, A. Merodio, J. Kwon, S. Okabe, and H.B. Kwon. 2025. Intercellular communication in the brain through a dendritic nanotubular network. *Science*. 390:eadr7403. https://doi.org/10.1126/science.adr7403

Chang, M., O.C. Lee, G. Bu, J. Oh, N.O. Yunn, S.H. Ryu, H.B. Kwon, A.B. Kolomeisky, S.H. Shim, J. Doh, et al. 2022. Formation of cellular close-ended tunneling nanotubes through mechanical deformation. *Sci Adv.* 8: eabj3995. https://doi.org/10.1126/sciadv.abj3995

Chang, X., and W.X. Wang. 2025. Passing the parcels: Intercellular nanoplastics transfer in mussels *Perna viridis* with activated immunomodulation. *Environ. Sci. Technol.* 59:8177–8188. https://doi.org/10.1021/acs.est.4c14465

Chauhan, B.K., A. Disanza, S.Y. Choi, S.C. Faber, M. Lou, H.E. Beggs, G. Scita, Y. Zheng, and R.A. Lang. 2009. Cdc42- and IRSp53-dependent contractile filopodia tether presumptive lens and retina to coordinate epithelial invagination. *Development*. 136:3657–3667. https://doi.org/10.1242/dev.042242

Chauveau, A., A. Aucher, P. Eissmann, E. Vivier, and D.M. Davis. 2010. Membrane nanotubes facilitate long-distance interactions between natural killer cells and target cells. *Proc. Natl. Acad. Sci. USA*. 107: 5545–5550. https://doi.org/10.1073/pnas.0910074107

Che, J., Y. Cheng, X. Wu, Z. Wu, L. Shang, and Y. Zhao. 2025a. M-Sec overexpressed stem cells growing abundant tunneling nanotubes for diverse active transferring. *ACS Nano*. 19:28644–28659. https://doi.org/10.1021/acsnano.5c08001

Che, Y., Y. Shimizu, T. Hayashi, J. Suzuki, Z. Pu, K. Tsuzuki, S. Narita, Y. Yura, R. Shibata, and T. Murohara. 2025b. Mitochondrial transfer from adipose-derived regenerative cells contributes therapeutic angiogenesis in a murine hindlimb ischemia model. *Angiogenesis*. 28:49. https://doi.org/10.1007/s10456-025-10001-z

Chen, B., X. Chen, J. Li, R. Hu, L. Yang, H. Li, X. Liu, R.D. Cannon, R. Saffery, B. Novakovic, et al. 2025a. Tunneling nanotube-mediated stem cell immunomodulation dysfunction promotes adipose inflammation and insulin resistance in GDM. *Cell Rep.* 44:116505. https://doi.org/10.1016/j.celrep.2025.116505

Chen, H., Z. Wu, L. Wang, J. Zeng, and T. Chen. 2025b. Cofilin is a key regulator of oxidative stress-induced intercellular tunneling nanotubes formation. *Int. J. Biochem. Cell Biol.* 186:106820. https://doi.org/10.1016/j.biocel.2025.106820

Chen, M., and D. Zhao. 2024. Invisible bridges: Unveiling the role and prospects of tunneling nanotubes in cancer therapy. *Mol. Pharm.* 21: 5413–5429. https://doi.org/10.1021/acs.molpharmaceut.4c00563

Chen, W., H. Huang, R. Hatori, and T.B. Kornberg. 2017. Essential basal cytonemes take up hedgehog in the *Drosophila* wing imaginal disc. *Development*. 144:3134–3144. https://doi.org/10.1242/dev.149856

Cohen, M., M. Georgiou, N.L. Stevenson, M. Miodownik, and B. Baum. 2010. Dynamic filopodia transmit intermittent delta-Notch signaling to drive pattern refinement during lateral inhibition. *Dev. Cell*. 19:78–89. https://doi.org/10.1016/j.devcel.2010.06.006

Cole, J.M., R. Dahl, and K.D. Cowden Dahl. 2021. MAPK signaling is required for generation of tunneling nanotube-like structures in ovarian cancer cells. *Cancers (Basel)*. 13:274. https://doi.org/10.3390/cancers13020274

da Silva, B., B.K. Irving, E.S. Polson, A. Droop, H.B.S. Griffiths, R.K. Mathew, L.F. Stead, J. Marrison, C. Williams, J. Williams, et al. 2019. Chemically induced neurite-like outgrowth reveals a multicellular network function in patient-derived glioblastoma cells. *J. Cell Sci.* 132:jcs228452. https://doi.org/10.1242/jcs.228452

Dagar, S., D. Pathak, H.V. Oza, and S.V.S. Mylavarapu. 2021a. Tunneling nanotubes and related structures: Molecular mechanisms of formation and function. *Biochem. J.* 478:3977–3998. https://doi.org/10.1042/BCJ20210077

Dagar, S., K. Pushpa, D. Pathak, S. Samaddar, A. Saxena, S. Banerjee, and S.V.S. Mylavarapu. 2021b. Nucleolin regulates 14-3-3ζ mRNA and promotes cofilin phosphorylation to induce tunneling nanotube formation. *FASEB J.* 35:e21199. https://doi.org/10.1096/fj.202001152R

Dash, C., T. Saha, S. Sengupta, and H.L. Jang. 2021. Inhibition of tunneling nanotubes between cancer cell and the endothelium alters the metastatic phenotype. *Int. J. Mol. Sci.* 22:6161. https://doi.org/10.3390/ijms22116161

D'Aloia, A., E. Arrigoni, B. Costa, G. Berruti, E. Martegani, E. Sacco, and M. Ceriani. 2021. RalGPS2 interacts with Akt and PDK1 promoting tunneling nanotubes formation in bladder cancer and kidney cells microenvironment. *Cancers*. 13:6330. https://doi.org/10.3390/cancers13246330

De Joussineau, C., J. Soulé, M. Martin, C. Anguille, P. Montcourrier, and D. Alexandre. 2003. Delta-promoted filopodia mediate long-range lateral inhibition in *Drosophila*. *Nature*. 426:555–559. https://doi.org/10.1038/nature02157

de Rooij, B., R. Polak, F. Stalpers, R. Pieters, and M.L. den Boer. 2017. Tunneling nanotubes facilitate autophagosome transfer in the leukemic niche. *Leukemia*. 31:1651–1654. https://doi.org/10.1038/leu.2017.117

Desir, S., E.L. Dickson, R.I. Vogel, V. Thayanithy, P. Wong, D. Teoh, M.A. Geller, C.J. Steer, S. Subramanian, and E. Lou. 2016. Tunneling nanotube formation is stimulated by hypoxia in ovarian cancer cells. *Oncotarget*. 7: 43150–43161. https://doi.org/10.18632/oncotarget.9504

Desir, S., P. O'Hare, R.I. Vogel, W. Sperduto, A. Sarkari, E.L. Dickson, P. Wong, A.C. Nelson, Y. Fong, C.J. Steer, et al. 2018. Chemotherapy-induced tunneling nanotubes mediate intercellular drug efflux in pancreatic cancer. *Sci. Rep.* 8:9484. https://doi.org/10.1038/s41598-018-27649-x

Desir, S., P. Wong, T. Turbyville, D. Chen, M. Shetty, C. Clark, E. Zhai, Y. Romin, K. Manova-Todorova, T.K. Starr, et al. 2019. Intercellular transfer of oncogenic KRAS via tunneling nanotubes introduces intracellular mutational heterogeneity in colon cancer cells. *Cancers (Basel)*. 11:892. https://doi.org/10.3390/cancers11070892

Du, L., A. Sohr, G. Yan, and S. Roy. 2018. Feedback regulation of cytoneme-mediated transport shapes a tissue-specific FGF morphogen gradient. *Elife*. 7:e38137. https://doi.org/10.7554/eLife.38137

Feng, T., Q. Xu, S. Wang, D. Hou, and X. Wu. 2025. Interplay between tunneling nanotubes and Wnt signaling: Insights into cytoskeletal

regulation and therapeutic potential. *Biochem. Biophys. Rep.* 43:102065. https://doi.org/10.1016/j.bbrep.2025.102065

Formicola, B., A. D'Aloia, R.D. Magro, S. Stucchi, R. Rigolio, M. Ceriani, and F. Re. 2019. Differential exchange of multifunctional liposomes between glioblastoma cells and healthy astrocytes via tunneling nanotubes. *Front. Bioeng. Biotechnol.* 7:403. https://doi.org/10.3389/fbioe.2019.00403

Franchi, M., Z. Piperigkou, E. Riti, V. Masola, M. Onisto, and N.K. Karamanos. 2020. Long filopodia and tunneling nanotubes define new phenotypes of breast cancer cells in 3D cultures. *Matrix Biol. Plus*. 6:100026. https://doi.org/10.1016/j.mbplus.2020.100026

Fu, Z., and Y. Yuan. 2024. TNFAIP2 as an emerging therapeutic target in cancer therapy and its underlying mechanisms. *Pharmacol. Res.* 204:107199. https://doi.org/10.1016/j.phrs.2024.107199

Genna, A., C.L. Duran, D. Entenberg, J.S. Condeelis, and D. Cox. 2023. Macrophages promote tumor cell extravasation across an endothelial barrier through thin membranous connections. *Cancers (Basel)*. 15:2092. https://doi.org/10.3390/cancers15072092

Gong, Z., T. Wu, Y. Zhao, J. Guo, Y. Zhang, B. Li, and Y. Li. 2025. Intercellular tunneling nanotubes as natural biophotonic conveyors. *ACS Nano*. 19:1036–1043. https://doi.org/10.1021/acsnano.4c12681

Gousset, K., L. Marzo, P.H. Commere, and C. Zurzolo. 2013. Myo10 is a key regulator of TNT formation in neuronal cells. *J. Cell Sci.* 126:4424–4435. https://doi.org/10.1242/jcs.129239

Halasz, H., V. Tarnai, J. Matko, M. Nyitrai, and E. Szabo-Meleg. 2024. Cooperation of various cytoskeletal components orchestrates intercellular spread of mitochondria between B-Lymphoma cells through tunnelling nanotubes. *Cells*. 13:607. https://doi.org/10.3390/cells13070607

Hall, E.T., M.E. Dillard, E.R. Cleverdon, Y. Zhang, C.A. Daly, S.S. Ansari, R. Wakefield, D.P. Stewart, S.M. Pruett-Miller, A. Lavado, et al. 2024. Cytoneme signaling provides essential contributions to mammalian tissue patterning. *Cell*. 187:276–293.e23. https://doi.org/10.1016/j.cell.2023.12.003

Hall, E.T., M.E. Dillard, D.P. Stewart, Y. Zhang, B. Wagner, R.M. Levine, S.M. Pruett-Miller, A. Sykes, J. Temirov, R.E. Cheney, et al. 2021. Cytoneme delivery of Sonic Hedgehog from ligand-producing cells requires Myosin 10 and a Dispatched-BOC/CDON co-receptor complex. *Elife*. 10:e61432. https://doi.org/10.7554/eLife.61432

Hanna, S.J., K. McCoy-Simandle, E. Leung, A. Genna, J. Condeelis, and D. Cox. 2019. Tunneling nanotubes, a novel mode of tumor cell-macrophage communication in tumor cell invasion. *J. Cell Sci.* 132:jcs223321. https://doi.org/10.1242/jcs.223321

Hanna, S.J., K. McCoy-Simandle, V. Miskolci, P. Guo, M. Cammer, L. Hodgson, and D. Cox. 2017. The role of Rho-GTPases and actin polymerization during macrophage tunneling nanotube biogenesis. *Sci. Rep.* 7:8547. https://doi.org/10.1038/s41598-017-08950-7

Hase, K., S. Kimura, H. Takatsu, M. Ohmae, S. Kawano, H. Kitamura, M. Ito, H. Watarai, C.C. Hazelett, C. Yeaman, and H. Ohno. 2009. M-Sec promotes membrane nanotube formation by interacting with Ral and the exocyst complex. *Nat. Cell Biol.* 11:1427–1432. https://doi.org/10.1038/ncb1990

Hein, M., H. Qambari, P. Yu, D.Y. Yu, and C. Balaratnasingam. 2024. Interpericyte tunneling nanotubes are nonuniformly distributed in the human macula. *Invest. Ophthalmol. Vis. Sci.* 65:28. https://doi.org/10.1167/iovs.65.13.28

Henderson, J.M., N. Ljubojevic, S. Belian, T.C. ChazeZurzolo, A. Battistella, Q. Giai Gianetto, M. Matondo, S. Descroix, and P. Bassereau. 2023. Tunnelling nanotube formation is driven by Eps8/IRSp53-dependent linear actin polymerization. *EMBO J.* 42:e113761. https://doi.org/10.15252/embj.2023113761

Hole, K.L., R. Norkett, E. Russell, P. Cottilli, M. Strom, J.H. Howden, N.J. Corbett, J. Brownlees, and M.J. Devine. 2026. MitoTracker transfers from astrocytes to neurons independently of mitochondria. *Cell Rep. Methods*. 6:101338. https://doi.org/10.1016/j.crmeth.2026.101338

Hoover, G., S. Gilbert, O. Curley, C. Obellianne, M.T. Lin, W. Hixson, T.W. Pierce, J.F. Andrews, M.F. Alexeyev, Y. Ding, et al. 2025. Nerve-to-cancer transfer of mitochondria during cancer metastasis. *Nature*. 644:252–262. https://doi.org/10.1038/s41586-025-09176-8

Hsiung, F., F.A. Ramirez-Weber, D.D. Iwaki, and T.B. Kornberg. 2005. Dependence of *Drosophila* wing imaginal disc cytonemes on decapentaplegic. *Nature*. 437:560–563. https://doi.org/10.1038/nature03951

Hu, B., J.J. Rodriguez, A. Kakkerla Balaraju, Y. Gao, N.T. Nguyen, H. Steen, S. Suhaib, S. Chen, and F. Lin. 2021. Glypican 4 mediates Wnt transport between germ layers via signaling filopodia. *J. Cell Biol.* 220:e202009082. https://doi.org/10.1083/jcb.202009082

Hu, H.T., T. Nishimura, H. Kawana, R.A.S. Dante, G. D'Angelo, and S. Suetsugu. 2024. The cellular protrusions for inter-cellular material transfer: Similarities between filopodia, cytonemes, tunneling nanotubes, viruses, and extracellular vesicles. *Front. Cell Dev. Biol.* 12:1422227. https://doi.org/10.3389/fcell.2024.1422227

Huang, H., and T.B. Kornberg. 2015. Myoblast cytonemes mediate Wg signaling from the wing imaginal disc and Delta-Notch signaling to the air sac primordium. *Elife*. 4:e06114. https://doi.org/10.7554/elife.06114

Huang, Q., B. Hu, P. Zhang, Y. Yuan, S. Yue, X. Chen, J. Liang, Z. Tang, and B. Zhang. 2025. Neuroscience of cancer: Unraveling the complex interplay between the nervous system, the tumor and the tumor immune microenvironment. *Mol. Cancer*. 24:24. https://doi.org/10.1186/s12943-024-02219-0

Ikeda, H., K. Kawase, T. Nishi, T. Watanabe, K. Takenaga, T. Inozume, T. Ishino, S. Aki, J. Lin, S. Kawashima, et al. 2025. Immune evasion through mitochondrial transfer in the tumour microenvironment. *Nature*. 638:225–236. https://doi.org/10.1038/s41586-024-08439-0

Jana, A., K. Ladner, E. Lou, and A.S. Nain. 2022. Tunneling nanotubes between cells migrating in ECM mimicking fibrous environments. *Cancers*. 14:1989. https://doi.org/10.3390/cancers14081989

Jansens, R.J.J., A. Tishchenko, and H.W. Favoreel. 2020. Bridging the gap: Virus long-distance spread via tunneling nanotubes. *J. Virol.* 94:e02120-19. https://doi.org/10.1128/jvi.02120-19

Joseph, J.V., C.R. Magaut, S. Storevik, L.H. Geraldo, T. Mathivet, M.A. Latif, J. Rudewicz, J. Guyon, M. Gambaretti, F. Haukas, et al. 2022. TGF-beta promotes microtube formation in glioblastoma through thrombospondin 1. *Neuro. Oncol.* 24:541–553. https://doi.org/10.1093/neuonc/noab212

Jung, E., J. Alfonso, H. Monyer, W. Wick, and F. Winkler. 2020. Neuronal signatures in cancer. *Int. J. Cancer*. 147:3281–3291. https://doi.org/10.1002/ijc.33138

Jung, E., M. Osswald, J. Blaes, B. Winkler, F. Sahm, T. Schmenger, G. Solecki, K. Deumelandt, F. T. Kurz, R. Xie, et al. 2017. Tweety-Homolog 1 drives brain colonization of gliomas. *J. Neurosci.* 37:6837–6857. https://doi.org/10.1523/JNEUROSCI.3532-16.2017

Kempf, S., R. Popp, Z. Naeem, T. Frömel, I. Wittig, S. Klatt, and I. Fleming. 2024. Pericyte-to-endothelial cell communication via tunneling nanotubes is disrupted by a diol of docosahexaenoic acid. *Cells*. 13:1429. https://doi.org/10.3390/cells13171429

Khattar, K., J. Safi, A. Rodriguez, and M. Vignais. 2022. Intercellular communication in the brain through tunneling nanotubes. *Cancers*. 14:1207. https://doi.org/10.3390/cancers14051207

Kolba, M.D., W. Dudka, M. Zareba-Koziol, A. Kominek, P. Ronchi, L. Turos, P. Chroscicki, J. Wlodarczyk, Y. Schwab, A. Klejman, et al. 2019. Tunneling nanotube-mediated intercellular vesicle and protein transfer in the stroma-provided imatinib resistance in chronic myeloid leukemia cells. *Cell Death Dis.* 10:817. https://doi.org/10.1038/s41419-019-2045-8

Korenkova, O., S. Liu, I. Prlesi, A. Pepe, S. Albadri, F. Del Bene, and C. Zurzolo. 2025. Tunneling nanotubes enable intercellular transfer in zebrafish embryos. *Dev. Cell*. 60:524–534.e3. https://doi.org/10.1016/j.devcel.2024.10.016

Korenkova, O., A. Pepe, and C. Zurzolo. 2020. Fine intercellular connections in development: TNTs, cytonemes, or intercellular bridges? *Cell Stress*. 4:30–43. https://doi.org/10.15698/cst2020.02.212

Kretschmer, A., F. Zhang, S.P. Somasekharan, C. Tse, L. Leachman, A. Gleave, B. Li, I. Asmaro, T. Huang, L. Kotula, et al. 2019. Stress-induced tunneling nanotubes support treatment adaptation in prostate cancer. *Sci. Rep.* 9:7826. https://doi.org/10.1038/s41598-019-44346-5

Latario, C.J., L.W. Schoenfeld, C.L. Howarth, L.E. Pickrell, F. Begum, D.A. Fischer, O. Grbovic-Huezo, S.D. Leach, Y. Sanchez, K.D. Smith, and H.N. Higgs. 2020. Tumor microtubes connect pancreatic cancer cells in an Arp2/3 complex-dependent manner. *Mol. Biol. Cell*. 31:1259–1272. https://doi.org/10.1091/mbc.E19-11-0605

Lee, C.-W., C.-C. Kuo, C.-J. Liang, H.-J. Pan, C.-N. Shen, and C.-H. Lee. 2022. Effects of the media conditioned by various macrophage subtypes derived from THP-1 cells on tunneling nanotube formation in pancreatic cancer cells. *BMC Mol. Cell Biol.* 23:26. https://doi.org/10.1186/s12860-022-00428-3

Liang, Z., S. Zhao, Y. Liu, and C. Cheng. 2025. The promise of mitochondria in the treatment of glioblastoma: A brief review. *Discover Oncol.* 16:142. https://doi.org/10.1007/s12672-025-01891-y

Libring, S., E.D. Berestesky, and C.A. Reinhart-King. 2024. The movement of mitochondria in breast cancer: Internal motility and intercellular transfer of mitochondria. *Clin. Exp. Metastasis*. 41:567–587. https://doi.org/10.1007/s10585-024-10269-3

Liu, Z., R. Joshi, Z. Zhou, F. Liu, Y. Gong, M. Sun, X. Li, T. Jiang, L. Zou, S. Wang, et al. 2025. Self-driven electrical triggering system activates tunneling nanotube highways to enhance drug delivery in bladder cancer therapy. *Nat. Commun.* 16:10093. https://doi.org/10.1038/s41467-025-65017-2

Ljubojevic, N., J.M. Henderson, and C. Zurzolo. 2021. The ways of actin: Why tunneling nanotubes are unique cell protrusions. *Trends Cell Biol.* 31: 130–142. https://doi.org/10.1016/j.tcb.2020.11.008

Lou, E., S. Fujisawa, A. Morozov, A. Barlas, Y. Romin, Y. Dogan, S. Gholami, A.L. Moreira, K. Manova-Todorova, and M.A. Moore. 2012. Tunneling nanotubes provide a unique conduit for intercellular transfer of cellular contents in human malignant pleural mesothelioma. *PLoS One*. 7: e33093. https://doi.org/10.1371/journal.pone.0033093

Lou, E., C. Verollet, F. Winkler, C. Zurzolo, S. Valdebenito-Silva, and E. Eugenin. 2024. Tunneling nanotubes and tumor microtubes-Emerging data on their roles in intercellular communication and pathophysiology: Summary of an international FASEB catalyst conference October 2023. *FASEB J.* 38:e23514. https://doi.org/10.1096/fj.202302551

Lu, J., X. Zheng, F. Li, Y. Yu, Z. Chen, Z. Liu, Z. Wang, H. Xu, and W. Yang. 2017. Tunneling nanotubes promote intercellular mitochondria transfer followed by increased invasiveness in bladder cancer cells. *Oncotarget*. 8:15539–15552. https://doi.org/10.18632/oncotarget.14695

Lu, J.J., W.M. Yang, F. Li, W. Zhu, and Z. Chen. 2019. Tunneling nanotubes mediated microRNA-155 intercellular transportation promotes bladder cancer cells' invasive and proliferative capacity. *Int. J. Nanomedicine*. 14: 9731–9743. https://doi.org/10.2147/IJN.S217277

Luz, M., S. Spannl-Müller, G. Ozhan, B. Kagermeier-Schenk, M. Rhinn, G. Weidinger, and M. Brand. 2014. Dynamic association with donor cell filopodia and lipid-modification are essential features of Wnt8a during patterning of the zebrafish neuroectoderm. *PLoS One*. 9:e84922. https://doi.org/10.1371/journal.pone.0084922

Lv, W., Z. Li, S. Wang, J. He, and L. Zhang. 2024. A role for tunneling nanotubes in virus spread. *Front. Microbiol.* 15:1356415. https://doi.org/10.3389/fmicb.2024.1356415

Ma, J., H. Yu, S. Yao, Y. Yan, Z. Gu, Z. Wang, H. Huang, and D. Chen. 2025. Making cells inter-connected for signaling communication: A developmental view of cytonemes. *Cell Commun. Signal.* 23:241. https://doi.org/10.1186/s12964-025-02229-5

Madarasz, T., B. Brunner, H. Halasz, E. Telek, J. Matko, M. Nyitrai, and E. Szabo-Meleg. 2023. Molecular relay stations in membrane nanotubes: IRSp53 involved in Actin-based force generation. *Int. J. Mol. Sci.* 24: 13112. https://doi.org/10.3390/ijms241713112

Magnon, C., and H. Hondermarck. 2023. The neural addiction of cancer. *Nat. Rev. Cancer*. 23:317–334. https://doi.org/10.1038/s41568-023-00556-8

Marlein, C.R., R.E. Piddock, J.J. Mistry, L. Zaitseva, C. Hellmich, R.H. Horton, Z. Zhou, M.J. Auger, K.M. Bowles, and S.A. Rushworth. 2019. CD38-driven mitochondrial trafficking promotes bioenergetic plasticity in multiple myeloma. *Cancer Res.* 79:2285–2297. https://doi.org/10.1158/0008-5472.CAN-18-0773

Marlein, C.R., L. Zaitseva, R.E. Piddock, S.D. Robinson, D.R. Edwards, M.S. Shafat, Z. Zhou, M. Lawes, K.M. Bowles, and S.A. Rushworth. 2017. NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. *Blood*. 130: 1649–1660. https://doi.org/10.1182/blood-2017-03-772939

Matejka, N., A. Amarlou, J. Neubauer, S. Rudigkeit, and R. Judith. 2024. High-resolution microscopic characterization of tunneling nanotubes in living U87 MG and LN229 glioblastoma cells. *Cells*. 13:464. https://doi.org/10.3390/cells13050464

Matula, Z., G. Mikala, S. Lukácsi, J. Matko, T. Kovacs, E. Monostori, F. Uher, and I. Valyi-Nagy. 2021. Stromal cells serve drug resistance for multiple myeloma via mitochondrial transfer: A study on primary myeloma and stromal cells. *Cancers (Basel)*. 13:3461. https://doi.org/10.3390/cancers13143461

Miao, L., Y. Lu, A. Nusrat, G. Fan, S. Zhang, L. Zhao, C.L. Wu, H. Guo, T.L.N. Huyen, Y. Zheng, et al. 2025. Tunneling nanotube-like structures regulate distant cellular interactions during heart formation. *Science* 387: eadd3417. https://doi.org/10.1126/science.add3417

Michita, R.T., L.B. Tran, S.J. Bark, D. Kumar, S.A. Toner, J. Jose, I.U. Mysorekar, and A. Narayanan. 2025. Zika virus NS1 drives tunneling nanotube formation for mitochondrial transfer and stealth transmission in trophoblasts. *Nat. Commun.* 16:1803. https://doi.org/10.1038/s41467-025-56927-2

Nahacka, Z., J. Novak, R. Zobalova, and J. Neuzil. 2022. Miro proteins and their role in mitochondrial transfer in cancer and beyond. *Front. Cell Dev. Biol.* 10:937753. https://doi.org/10.3389/fcell.2022.937753

Nazari, S.S., A.D. Doyle, C.K.E. Bleck, and K.M. Yamada. 2023. Long prehensile protrusions can facilitate cancer cell invasion through the basement membrane. *Cells*. 12:2474. https://doi.org/10.3390/cells12202474

Nobes, C.D., and A. Hall. 1995. Rho, rac, and cdc42 GTPases regulate the assembly of multimolecular focal complexes associated with actin stress fibers, lamellipodia, and filopodia. *Cell*. 81:53–62. https://doi.org/10.1016/0092-8674(95)90370-4

Notario Manzano, R., T. Chaze, E. Rubinstein, E. Penard, M. Matondo, C. Zurzolo, and C. Brou. 2024. Proteomic landscape of tunneling nanotubes reveals CD9 and CD81 tetraspanins as key regulators. *Elife*. 13: RP99172. https://doi.org/10.7554/eLife.99172

Omsland, M., V. Andresen, S.E. Gullaksen, P. Ayuda-Durán, M. Popa, R. Hovland, A. Brendehaug, J. Enserink, E. McCormack, and B.T. Gjertsen. 2020. Tyrosine kinase inhibitors and interferon-alpha increase tunneling nanotube (TNT) formation and cell adhesion in chronic myeloid leukemia (CML) cell lines. *FASEB J.* 34:3773–3791. https://doi.org/10.1096/fj.201802061RR

Omsland, M., Ø. Bruserud, B.T. Gjertsen, and V. Andresen. 2017. Tunneling nanotube (TNT) formation is downregulated by cytarabine and NF-κB inhibition in acute myeloid leukemia (AML). *Oncotarget*. 8:7946–7963. https://doi.org/10.18632/oncotarget.13853

Önfelt, B., S. Nedvetzki, R. Benninger, M. Purbhoo, S. Sowinski, N.H. Alistair, M. Seabra, M. Neil, P. French, and D. Davis. 2006. Structurally distinct membrane nanotubes between human macrophages support long-distance vesicular traffic or surfing of bacteria1. *The J. Immunol.* 177: 8476–8483. https://doi.org/10.4049/jimmunol.177.12.8476

Osswald, M., E. Jung, F. Sahm, G. Solecki, V. Venkataramani, J. Blaes, S. Weil, H. Horstmann, B. Wiestler, M. Syed, et al. 2015. Brain tumour cells interconnect to a functional and resistant network. *Nature*. 528:93–98. https://doi.org/10.1038/nature16071

Ota, R., and K. Nagayama. 2025. Atomic force microscopy estimation of mechanical properties of tunneling nanotubes in cancer cells. *Adv. Biomed. Eng.* 14:70–78. https://doi.org/10.14326/abe.14.70

Ottonelli, I., R. Caraffi, G. Tosi, M.A. Vandelli, J. Duskey, and B. Ruozi. 2022. Tunneling nanotubes: A new target for nanomedicine? *Int. J. Mol. Sci.* 23: 2237. https://doi.org/10.3390/ijms23042237

Palese, F., M. Rakotobe, and C. Zurzolo. 2025. Transforming the concept of connectivity: Unveiling tunneling nanotube biology and their roles in brain development and neurodegeneration. *Physiol. Rev.* 105:1823–1865. https://doi.org/10.1152/physrev.00023.2024

Parker, I., K.T. Evans, K. Ellefsen, D.A. Lawson, and I.F. Smith. 2017. Lattice light sheet imaging of membrane nanotubes between human breast cancer cells in culture and in brain metastases. *Sci. Rep.* 7:11029. https://doi.org/10.1038/s41598-017-11223-y

Pasquier, J., L. Galas, C. Boulangé-Lecomte, D. Rioult, F. Bultelle, P. Magal, G. Webb, and F. Le Foll. 2012. Different modalities of intercellular membrane exchanges mediate cell-to-cell p-glycoprotein transfers in MCF-7 breast cancer cells. *J. Biol. Chem.* 287:7374–7387. https://doi.org/10.1074/jbc.M111.312157

Patel, A., Y. Wu, X. Han, Y. Su, T. Maugel, H. Shroff, and S. Roy. 2022. Cytonemes coordinate asymmetric signaling and organization in the *Drosophila* muscle progenitor niche. *Nat. Commun.* 13:1185. https://doi.org/10.1038/s41467-022-28587-z

Pepe, A., S. Pietropaoli, M. Vos, G. Barba-Spaeth, and C. Zurzolo. 2022. Tunneling nanotubes provide a route for SARS-CoV-2 spreading. *Sci. Adv.* 8:eabo0171. https://doi.org/10.1126/sciadv.abo0171

Pergu, R., S. Dagar, H. Kumar, R. Kumar, J. Bhattacharya, and S.V.S. Mylavarapu. 2019. The chaperone ERp29 is required for tunneling nanotube formation by stabilizing MSec. *J. Biol. Chem.* 294:7177–7193. https://doi.org/10.1074/jbc.RA118.005659

Pinto, G., C. Brou, and C. Zurzolo. 2020. Tunneling nanotubes: The fuel of tumor progression? *Trends Cancer*. 6:874–888. https://doi.org/10.1016/j.trecan.2020.04.012

Pinto, G., I. Saenz-de-Santa-Maria, P. Chastagner, E. Perthame, C. Delmas, C. Toulas, E. Moyal-Jonathan-Cohen, C. Brou, and C. Zurzolo. 2021. Patient-derived glioblastoma stem cells transfer mitochondria through tunneling nanotubes in tumor organoids. *Biochem. J.* 478:21–39. https://doi.org/10.1042/BCJ20200710

Polak, R., B. de Rooij, R. Pieters, and M.L. den Boer. 2015. B-cell precursor acute lymphoblastic leukemia cells use tunneling nanotubes to orchestrate their microenvironment. *Blood*. 126:2404–2414. https://doi.org/10.1182/blood-2015-03-634238

Pulze, L., T. Congiu, T.A.L. Brevini, A. Grimaldi, G. Tettamanti, P. D'Antona, N. Baranzini, F. Acquati, F. Ferraro, and M. de Eguileor. 2020. MCF7

spheroid development: New insight about spatio/temporal arrangements of TNTs, amyloid fibrils, cell connections, and cellular bridges. *Int. J. Mol. Sci.* 21:5400. https://doi.org/10.3390/ijms21155400

Qin, Y., X. Jiang, Q. Yang, J. Zhao, Q. Zhou, and Y. Zhou. 2021. The functions, methods, and mobility of mitochondrial transfer between cells. *Front. Oncol.* 11:672781. https://doi.org/10.3389/fonc.2021.672781

Raghavan, A., R. Kashyap, P. Sreedevi, S. Jos, S. Chatterjee, A. Alex, M.N. D'Souza, M. Giridharan, R. Muddashetty, R. Manjithaya, S. Padavattan, and S. Nath. 2024. Astroglia proliferate upon the biogenesis of tunneling nanotubes via α-synuclein dependent transient nuclear translocation of focal adhesion kinase. *iScience*. 27:110565. https://doi.org/10.1016/j.isci.2024.110565

Raghunathan, A., R. Sivakamasundari, J. Wolenski, R. Poddar, and S.M. Weissman. 2001. Functional analysis of B144/LST1: A gene in the tumor necrosis factor cluster that induces formation of long filopodia in eukaryotic cells. *Exp. Cell Res.* 268:230–244. https://doi.org/10.1006/excr.2001.5290

Rakotobe, M., and C. Zurzolo. 2025. Beyond synapses: Cytoplasmic connections in brain function and evolution. *Biol. Rev. Camb. Philos. Soc.* 100:2055–2070. https://doi.org/10.1111/brv.70034

Ramírez-Weber, F.A., and T.B. Kornberg. 1999. Cytonemes: Cellular processes that project to the principal signaling center in *Drosophila* imaginal discs. *Cell*. 97:599–607. https://doi.org/10.1016/s0092-8674(00)80771-0

Roy, S., F. Hsiung, and T.B. Kornberg. 2011. Specificity of *Drosophila* cytonemes for distinct signaling pathways. *Science* 332:354–358. https://doi.org/10.1126/science.1198949

Roy, S., H. Huang, S. Liu, and T.B. Kornberg. 2014. Cytoneme-mediated contact-dependent transport of the *Drosophila* decapentaplegic signaling protein. *Science* 343:1244624. https://doi.org/10.1126/science.1244624

Rustom, A., R. Saffrich, I. Markovic, P. Walther, and H. Gerdes. 2004. Nanotubular highways for intercellular organelle transport. *Science*. 303:1007–1010. https://doi.org/10.1126/science.1093133

Sáenz-de-Santa-María, I., C. Bernardo-Castiñeira, E. Enciso, I. García-Moreno, C.J. L, C. Suarez, and M.-D. Chiara. 2017. Control of long-distance cell-to-cell communication and autophagosome transfer in squamous cell carcinoma via tunneling nanotubes. *Oncotarget*. 8:20939–20960. https://doi.org/10.18632/oncotarget.15467

Sagar, F. Pröls, C. Wiegreffe, and M. Scaal. 2015. Communication between distant epithelial cells by filopodia-like protrusions during embryonic development. *Development*. 142:665–671. https://doi.org/10.1242/dev.115964

Saha, T., C. Dash, R. Jayabalan, S. Khiste, A. Kulkarni, K. Kurmi, J. Mondal, P.K. Majumder, A. Bardia, H.L. Jang, and S. Sengupta. 2022. Intercellular nanotubes mediate mitochondrial trafficking between cancer and immune cells. *Nat. Nanotechnol.* 17:98–106. https://doi.org/10.1038/s41565-021-01000-4

Sakthivelu, V., A. Schmitt, F. Odenthal, K. Ndoci, M. Touet, A.H. Shaib, A. Chihab, G.A. Wani, P. Nieper, G.G. Hartmann, et al. 2025. Functional synapses between neurons and small cell lung cancer. *Nature*. 646:1243–1253. https://doi.org/10.1038/s41586-025-09434-9

Sanders, T.A., E. Llagostera, and M. Barna. 2013. Specialized filopodia direct long-range transport of SHH during vertebrate tissue patterning. *Nature*. 497:628–632. https://doi.org/10.1038/nature12157

Sarkari, A., S. Korenfeld, K. Deniz, K. Ladner, P. Wong, S. Padmanabhan, R.I. Vogel, L.A. Sherer, N. Courtemanche, C. Steer, et al. 2023. Treatment with tumor-treating fields (TTFields) suppresses intercellular tunneling nanotube formation in vitro and upregulates immuno-oncologic biomarkers in vivo in malignant mesothelioma. *Elife*. 12:e85383. https://doi.org/10.7554/eLife.85383

Sarkari, A., and E. Lou. 2024. Do tunneling nanotubes drive chemoresistance in solid tumors and other malignancies? *Biochem. Soc. Trans.* 52:1757–1764. https://doi.org/10.1042/BST20231364

Sartori-Rupp, A., D. Cordero Cervantes, A. Pepe, K. Gousset, E. Delage, S. Corroyer-Dulmont, C. Schmitt, J. Krijnse-Locker, and C. Zurzolo. 2019. Correlative cryo-electron microscopy reveals the structure of TNTs in neuronal cells. *Nat. Commun.* 10:342. https://doi.org/10.1038/s41467-018-08178-7

Sato, M., and T.B. Kornberg. 2002. FGF is an essential mitogen and chemoattractant for the air sacs of the *Drosophila* tracheal system. *Dev. Cell*. 3:195–207. https://doi.org/10.1016/s1534-5807(02)00202-2

Savchuk, S., K.M. Gentry, W. Wang, E. Carleton, C.A.O. Biagi-Junior, K. Luthria, B. Yalcin, L. Ni, H.C. Farnsworth, R.A. Davis, et al. 2025. Neuronal activity-dependent mechanisms of small cell lung cancer pathogenesis. *Nature*. 646:1232–1242. https://doi.org/10.1038/s41586-025-09492-z

Schiller, C., K.N. Diakopoulos, I. Rohwedder, E.E.H. KremmerWeiss, C. von Toerne, M. Ueffing, U.H. Weidle, and H. Ohno. 2013. LST1 promotes the assembly of a molecular machinery responsible for tunneling nanotube formation. *J. Cell Sci.* 126:767–777. https://doi.org/10.1242/jcs.114033

Sharma, M., and S. Subramaniam. 2019. Rhes travels from cell to cell and transports Huntington disease protein via TNT-like protrusion. *J. Cell Biol.* 218:1972–1993. https://doi.org/10.1083/jcb.201807068

Sherer, N.M., and W. Mothes. 2008. Cytonemes and tunneling nanotubules in cell-cell communication and viral pathogenesis. *Trends Cell Biol.* 18:414–420. https://doi.org/10.1016/j.tcb.2008.07.003

Sierri, G., I. Sáenz-de-Santa-María, A. Renda, M. Koch, P. Sommi, U. Anselmi-Tamburini, M. Mauri, A. D'Aloia, M. Ceriani, D. Salerno, et al. 2025. Nanoparticle shape is the game-changer for blood–brain barrier crossing and delivery through tunneling nanotubes among glioblastoma cells. *Nanoscale*. 17:992–1006. https://doi.org/10.1039/d4nr03174a

Simone, L., D.L. Capobianco, D. Di Cosimo, E. Battini, F.G. Livraghi, A. Vescovi, M. Svelto, and F. Pisani. 2023. GFAP serves as a structural element of tunneling nanotubes between glioblastoma cells and could play a role in the intercellular transfer of mitochondria. *Front. Cell Dev. Biol.* 11:1221671. https://doi.org/10.3389/fcell.2023.1221671

Sinha, S., B.W. Callow, A.P. Farfel, S. Roy, S. Chen, M. Masotti, S. Rajendran, J.M. Buschhaus, C.R. Espinoza, K.E. Luker, et al. 2024. Breast cancers that disseminate to bone marrow acquire aggressive phenotypes through CX43-related tumor-stroma tunnels. *J. Clin. Invest.* 134:e170953. https://doi.org/10.1172/JCI170953

Song, R., C. Huang, Y. Ma, Z. Zhang, Y. Liu, B. Chen, X. Zhang, S. Hao, H. Huang, M. Ashrafizadeh, et al. 2026. Cytoskeletal remodeling promotes tunneling nanotube formation and drives cardiac resident cell mitochondrial transfer in sepsis. *Sci. Adv.* 12:eadz3266. https://doi.org/10.1126/sciadv.adz3266

Sowinski, S., C. Jolly, O. Berninghausen, M.A. Purbhoo, A. Chauveau, K. Köhler, S. Oddos, P. Eissmann, F.M. Brodsky, C. Hopkins, et al. 2008. Membrane nanotubes physically connect T cells over long distances presenting a novel route for HIV-1 transmission. *Nat. Cell Biol.* 10:211–219. https://doi.org/10.1038/ncb1682

Stanganello, E., A.I.H. Hagemann, B. Mattes, C. Sinner, D. Meyen, S. Weber, A. Schug, E. Raz, and S. Scholpp. 2015. Filopodia-based Wnt transport during vertebrate tissue patterning. *Nat. Commun.* 6:5846. https://doi.org/10.1038/ncomms6846

Teddy, J.M., and P.M. Kulesa. 2004. In vivo evidence for short- and long-range cell communication in cranial neural crest cells. *Development*. 131:6141–6151. https://doi.org/10.1242/dev.01534

Tishchenko, A., D.D. Azorín, L. Vidal-Brime, M.J. Muñoz, P.J. Arenas, C. Pearce, H. Girão, S.R.y. Cajal, and T. Aasen. 2020. Cx43 and associated cell signaling pathways regulate tunneling nanotubes in breast cancer cells. *Cancers*. 12:2798. https://doi.org/10.3390/cancers12102798

Valdebenito, S., A. Audia, K.P.L. Bhat, G. Okafo, and E.A. Eugenin. 2020. Tunneling nanotubes mediate adaptation of glioblastoma cells to temozolomide and ionizing radiation treatment. *iScience*. 23:101450. https://doi.org/10.1016/j.isci.2020.101450

Valdebenito, S., S. Malik, R. Luu, O. Loudig, M. Mitchell, G. Okafo, K. Bhat, B. Prideaux, and E.A. Eugenin. 2021. Tunneling nanotubes, TNT, communicate glioblastoma with surrounding non-tumor astrocytes to adapt them to hypoxic and metabolic tumor conditions. *Sci. Rep.* 11:14556. https://doi.org/10.1038/s41598-021-93775-8

Vargas, J.Y., F. Loria, Y.J. Wu, G. Córdova, T. Nonaka, S. Bellow, S. Syan, M. Hasegawa, G.M. van Woerden, C. Trollet, and C. Zurzolo. 2019. The Wnt/Ca^{2+} pathway is involved in interneuronal communication mediated by tunneling nanotubes. *EMBO J.* 38:e101230. https://doi.org/10.15252/embj.2018101230

Venkataramani, V., M. Schneider, F.A. Giordano, T. Kuner, W. Wick, U. Herrlinger, and F. Winkler. 2022. Disconnecting multicellular networks in brain tumours. *Nat. Rev. Cancer*. 22:481–491. https://doi.org/10.1038/s41568-022-00475-0

Victoria, G.S., and C. Zurzolo. 2017. The spread of prion-like proteins by lysosomes and tunneling nanotubes: Implications for neurodegenerative diseases. *J. Cell Biol.* 216:2633–2644. https://doi.org/10.1083/jcb.201701047

Vidulescu, C., S. Clejan, and K.C. O'Connor. 2004. Vesicle traffic through intercellular bridges in DU 145 human prostate cancer cells. *J. Cell Mol. Med.* 8:388–396. https://doi.org/10.1111/j.1582-4934.2004.tb00328.x

Wang, T., L. Wang, J. Sun, Y. Chen, W. Ali, Y. Ma, R. Song, X. Tong, J. Zhu, Y. Yuan, et al. 2025a. Tunneling nanotube-mediated transcellular autophagy alleviates cadmium induced hepatocyte injury. *Adv. Sci. (Weinh)*. 12:e02793. https://doi.org/10.1002/advs.202502793

Wang, X., and H.H. Gerdes. 2015. Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. *Cell Death Differ.* 22:1181–1191. https://doi.org/10.1038/cdd.2014.211

Wang, Y., J. Cui, X. Sun, and Y. Zhang. 2011. Tunneling-nanotube development in astrocytes depends on p53 activation. *Cell Death Differ.* 18: 732–742. https://doi.org/10.1038/cdd.2010.147

Wang, Y., T. Nguyen, Q. He, O. Has, K. Forouzesh, and D.S. Eom. 2025b. Cytoneme-mediated intercellular signaling in keratinocytes is essential for epidermal remodeling in zebrafish. *Elife.* 13:RP97400. https://doi.org/10.7554/eLife.97400

Watkins, S.C., and R.D. Salter. 2005. Functional connectivity between immune cells mediated by tunneling nanotubules. *Immunity.* 23:309–318. https://doi.org/10.1016/j.immuni.2005.08.009

Watson, D.C., D. Bayik, S. Storevik, S.S. Moreino, S.A. Sprowls, J. Han, M.T. Augustsson, A. Lauko, P. Sravya, G.V. Rosland, et al. 2023. GAP43-dependent mitochondria transfer from astrocytes enhances glioblastoma tumorigenicity. *Nat. Cancer.* 4:648–664. https://doi.org/10.1038/s43018-023-00556-5

Weil, S., M. Osswald, G. Solecki, J. Grosch, E. Jung, D. Lemke, M. Ratliff, D. Hanggi, W. Wick, and F. Winkler. 2017. Tumor microtubes convey resistance to surgical lesions and chemotherapy in gliomas. *Neuro. Oncol.* 19:1316–1326. https://doi.org/10.1093/neuonc/nox070

Weir, D., C. Bentley-Abbot, J. McCowan, C. Loney, E. Roberts, and E. Hutchinson. 2025. Induction of tunnelling nanotube-like structures by influenza A viruses requires the onset of apoptosis. *PLoS Pathog.* 21: e1013191. https://doi.org/10.1371/journal.ppat.1013191

Wood, B.M., V. Baena, H. Huang, D.M. Jorgens, M. Terasaki, and T.B. Kornberg. 2021. Cytonemes with complex geometries and composition extend into invaginations of target cells. *J. Cell Biol.* 220:e202101116. https://doi.org/10.1083/jcb.202101116

Xie, R., T. Kessler, J. Grosch, L. Hai, V. Venkataramani, L. Huang, D.C. Hoffmann, G. Solecki, M. Ratliff, M. Schlesner, et al. 2021. Tumor cell network integration in glioma represents a stemness feature. *Neuro. Oncol.* 23:757–769. https://doi.org/10.1093/neuonc/noaa275

Yamada, K.M., and M. Sixt. 2019. Mechanisms of 3D cell migration. *Nat. Rev. Mol. Cell Biol.* 20:738–752. https://doi.org/10.1038/s41580-019-0172-9

Yamashita, Y.M., M. Inaba, and M. Buszczak. 2018. Specialized intercellular communications via cytonemes and nanotubes. *Annu. Rev. Cell Dev. Biol.* 34:59–84. https://doi.org/10.1146/annurev-cellbio-100617-062932

Zampieri, L.X., C. Silva-Almeida, J.D. Rondeau, and P. Sonveaux. 2021. Mitochondrial transfer in cancer: A comprehensive review. *Int. J. Mol. Sci.* 22:3245. https://doi.org/10.3390/ijms22063245

Zhang, C., L. Brunt, Y. Ono, S. Rogers, and S. Scholpp. 2024. Cytoneme-mediated transport of active Wnt5b-Ror2 complexes in zebrafish. *Nature.* 625:126–133. https://doi.org/10.1038/s41586-023-06850-7

Zhang, C., and R. Schekman. 2023. Syncytin-mediated open-ended membrane tubular connections facilitate the intercellular transfer of cargos including Cas9 protein. *Elife.* 12:e84391. https://doi.org/10.7554/eLife.84391

Zhang, W., J.A. DeMattia, H. Song, and W.T. Couldwell. 2003. Communication between malignant glioma cells and vascular endothelial cells through gap junctions. *J. Neurosurg.* 98:846–853. https://doi.org/10.3171/jns.2003.98.4.0846

Zhu, C., Y. Shi, and J. You. 2021. Immune cell connection by tunneling nanotubes: The impact of intercellular cross-talk on the immune response and its therapeutic applications. *Mol. Pharm.* 18:772–786. https://doi.org/10.1021/acs.molpharmaceut.0c01248

Zhu, S., S. Bhat, S. Syan, Y. Kuchitsu, M. Fukuda, and C. Zurzolo. 2018. Rab11a–Rab8a cascade regulates the formation of tunneling nanotubes through vesicle recycling. *J. Cell Sci.* 131:jcs216226. https://doi.org/10.1242/jcs.215889

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Supplemental material

Provided online are Table S1 and Table S2. Table S1 shows cytonemes in development. Table S2 shows tunneling nanotubes and cancer microtubes in various cancers.