



Review

# Channeling Force in the Brain: Mechanosensitive Ion Channels Choreograph Mechanics and Malignancies

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**Force is everywhere. Through cell-intrinsic activities and interactions with the microenvironment, cells generate, transmit, and sense mechanical forces, such as compression, tension, and shear stress. These forces shape the mechanical properties of cells and tissues. Akin to how balanced biochemical signaling safeguards physiological processes, a mechanical optimum is required for homeostasis. The brain constructs a mechanical optimum from its cellular and extracellular constituents. However, in brain cancer, the mechanical properties are disrupted: tumor and nontumoral cells experience dysregulated solid and fluid stress, while tumor tissue develops altered stiffness. Mechanosensitive (MS) ion channels perceive mechanical cues to govern ion flux and cellular signaling. In this review, we describe the mechanical properties of the brain in healthy and cancer states and illustrate MS ion channels as sensors of mechanical cues to regulate malignant growth. Targeting MS ion channels offers disease insights at the interface of cancer, neuroscience, and mechanobiology to reveal therapeutic opportunities in brain tumors.**

## Solid Stress in the Brain

**Tension** (see [Glossary](#)) and **compression** (Figure 1A), mechanical forces transmitted by **elastic** constituents, such as cells and the extracellular matrix (ECM), generate solid **stress**. Tension and compression have multifaceted roles in the nervous system. Tension at the axonal growth cone and its dissipation along neurites regulate axon growth [1]. Tension also strengthens synaptic formation during axon growth cone attachment to its target neuron [2]. Mechanical stretching, which applies tension, promotes neural stem cell differentiation toward neurons and enhances neurite extension parallel to the direction of the force [3], while decreasing the oligodendrocyte differentiation potential of neural stem cells [4]. Embryonic mouse cerebellum develops both circumferential and radial tension, which functions as a mechanical constraint to regulate cerebellar folding [5]. These studies show that tension can regulate neural network formation by controlling axonal growth and synaptic partnerships at the cellular level, and instruct brain patterning at the tissue level. While compression in weight-bearing tissues (e.g., bone or tendon) is well characterized to regulate cell behaviors and tissue properties, such as differentiation of osteoblasts and osteoclasts [6] and mechanical strength of tendons [7], its functional role in the brain remains largely undefined.

Conventionally, the brain is considered a mechanically inert organ that is not subjected to dynamic solid stress. However, magnetic resonance imaging (MRI) studies reveal macroscopic white matter movement with cardiac and respiratory cycles [8] and whole-brain pulsations with each systole and diastole [9]. These observations raise intriguing questions. What are the

## Highlights

Cellular and extracellular constituents establish a mechanical optimum in the brain at homeostasis.

Brain cancer reshapes microenvironmental forces and cellular and tissue mechanics.

MS ion channels sense mechanical cues, including solid stress, fluid shear stress, and tissue stiffness, to regulate tumor and nontumor cell behaviors.

Targeting MS ion channels reveals novel biology and therapeutic opportunities in brain cancer.

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spatiotemporal dynamics of cyclic compression and tension in the developing and adult brain? Do specific brain cell types perceive and respond to cyclic compression and tension? Do cyclic compression and tension functionally modulate brain development, homeostasis, and pathology? To date, our understanding of the role of solid stress in brain cells is primarily based on *in vitro* studies due to the lack of tools to precisely quantify and manipulate solid stress *in vivo*. Developing novel approaches to investigate these questions will provide insights into how solid stress regulates brain development and function.

### Solid Stress in Brain Cancer

Due to cell division, growth and movement in confined spaces, ECM dysregulation, and immune and stromal cell infiltration, cells generate, transmit, and experience pervasive solid stress in tumors [10–12]. Glioblastoma (GBM), the most aggressive primary brain tumor [13], develops intratumorally heterogeneous solid stress: GBM periphery and core experience tensile stress (0.04–0.21 kPa), while annular regions near the tumor periphery experience compressive stress (0.01–0.1 kPa) [14] (Figure 2). Aberrant compression can disrupt blood vessels to perturb nutrient and oxygen supply, leading to the formation of necrotic regions, which are frequently present in GBM [15]. Furthermore, compression-driven hypoxia increases Tenascin-C (a glycoprotein in the ECM) expression to elevate tissue **stiffness** (see the following stiffness sections) and promote tumor progression [16]. Additionally, locoregional compression in tumors results in poor drug perfusion to compromise chemotherapy efficacy [17] (Figure 2).

GBM can display nodular and infiltrative growth. Nodular growth results in balloon-like expansion of tumor mass, which applies solid stress to its surrounding tissues. Infiltrative growth incurs less solid stress because the tumor cells disperse into the brain parenchyma. As a result, compression and tension forces are more prominent around nodular than infiltrative GBM. In addition to impairing vascular structure and permeability, solid stress can induce neuronal death adjacent to the tumor mass, facilitating nontumoral tissue displacement by the expanding tumor mass [15,18] (Figure 2). Interestingly, *in vivo* release of solid stress restored vascular perfusion and neurological functions in GBM-bearing mice. Lithium chloride treatment was neuroprotective in these mice by reducing solid stress-induced neuronal death, thereby improving motor coordination [18]. While the underlying mechanism remains to be elucidated, this study supports the potential use of lithium treatment in patients bearing brain tumors with high solid stress. Despite distinct cells-of-origin and oncogenic mutations, various types of brain tumor display nodular and infiltrative growth. Unveiling the spatiotemporal dynamics of solid stress and how tumor and nontumoral cell types sense and respond to mechanical forces may offer insights to alleviate symptoms of patients with brain malignancies.

### Fluid Shear Stress in the Brain

Fluid **shear stress** (Figure 1A), the mechanical stress applied parallel to an object, can present in either laminar flow, in which fluid travels smoothly in a regular path, or turbulent flow, in which fluid travels irregularly with mixings and fluctuations. The brain harbors three types of biofluid: blood, interstitial fluid (ISF), and cerebrospinal fluid (CSF) (Figure 2). Blood shear stress, which varies widely in intensity (0.1–9 Pa, lowest in capillaries and highest in arteries), regulates endothelial cell alignment, permeability, and angiogenesis [19]. ISF is produced at the **blood–brain barrier** (BBB) and moved by pressure-dependent bulk flow through the extracellular space of brain parenchyma into brain ventricles and the subarachnoid space [20]. Produced by choroid plexus and ependymal cells, CSF fills brain ventricles, subarachnoid cisterns, and the central canal of the spinal cord. CSF movement is driven by cardiac rhythm and motile cilia of the ependymal cells. Quantitative MRI and computational modeling suggest that the CSF flow rate ranges from 1 mm/s in subarachnoid space and lateral ventricles to 14 mm/s in pontine cistern, exerting a

### Glossary

**Blood–brain barrier (BBB):** the brain capillary structure comprising endothelial cells, astrocyte endfeet, and pericytes, which allows regulated entry of selected macromolecules while preventing the crossing of most blood solubles and therapeutic agents.

**Blood–tumor barrier (BTB):** the brain barrier structure comprising the BBB and vasculature-interacting cancer cells.

**Cancer evolution:** the selection of mutations, which alters cell fitness in response to microenvironmental and therapeutic stress, shapes the clonal compositions in the lifetime of cancer.

**Compression:** axially transmitted force that increases the cross-sectional area and decreases the length of an object.

**Elastic:** description of the ability of a material to deform due to force, to transmit force, and to store elastic energy in the deformation.

**Extravasation:** cell movement from the lumen of a blood or lymphatic vessel into the surrounding tissue.

**Glymphatic system:** macroscopic waste clearance system that utilizes perivascular spaces to remove neurotoxic solubles and facilitate distribution of functional molecules in the brain.

**Intravasation:** cell movement through the basement membrane into the lumen of a blood or lymphatic vessel.

**Mechanical niche:** area of a tissue in which cells experience specific force and microenvironmental mechanical cues, which collectively regulate cell states and behaviors.

**Nuclear actin:** viscoelastic actin filament scaffold in the nucleoplasm that regulates chromatin stability and nuclear organizations.

**Nucleoskeleton (nuclear matrix):** filamented element mainly contributed by intermediate type V filaments, including lamins, myosins, actin, spectrins, and kinesins. It interacts with the cytoskeleton via the LINC complex.

**Rheology:** flow and deformation of fluid and solid materials under force.

**Shear stress:** force per unit area of the surface in parallel to force application direction (e.g., parallel to the surface of the cell).

**Stiffness:** degree to which the material resists deformation in response to an applied force.

**Stress:** force per unit area.

**Tension:** force per unit length acting on a cross-section of membrane.

shear stress of  $\sim 0.001$  Pa in lateral ventricles to  $\sim 1.6$  Pa along the aqueduct of Sylvius [21] (Figure 2). The combination of arterial pulsation, respiration, and CSF pressure gradients establishes the **glymphatic system**, in which a convective fluid flux travels through perivascular space of brain arteries into the loose fibrous matrix of the surrounding large deep veins. By allowing rapid and continuous exchange between CSF and ISF, the glymphatic system is a pathway to collect and remove neurotoxic protein aggregates and metabolic wastes, and distribute signaling molecules, neurotransmitters, and metabolites in the brain [22]. The physiological function of shear stress within the glymphatic system remains to be explored.

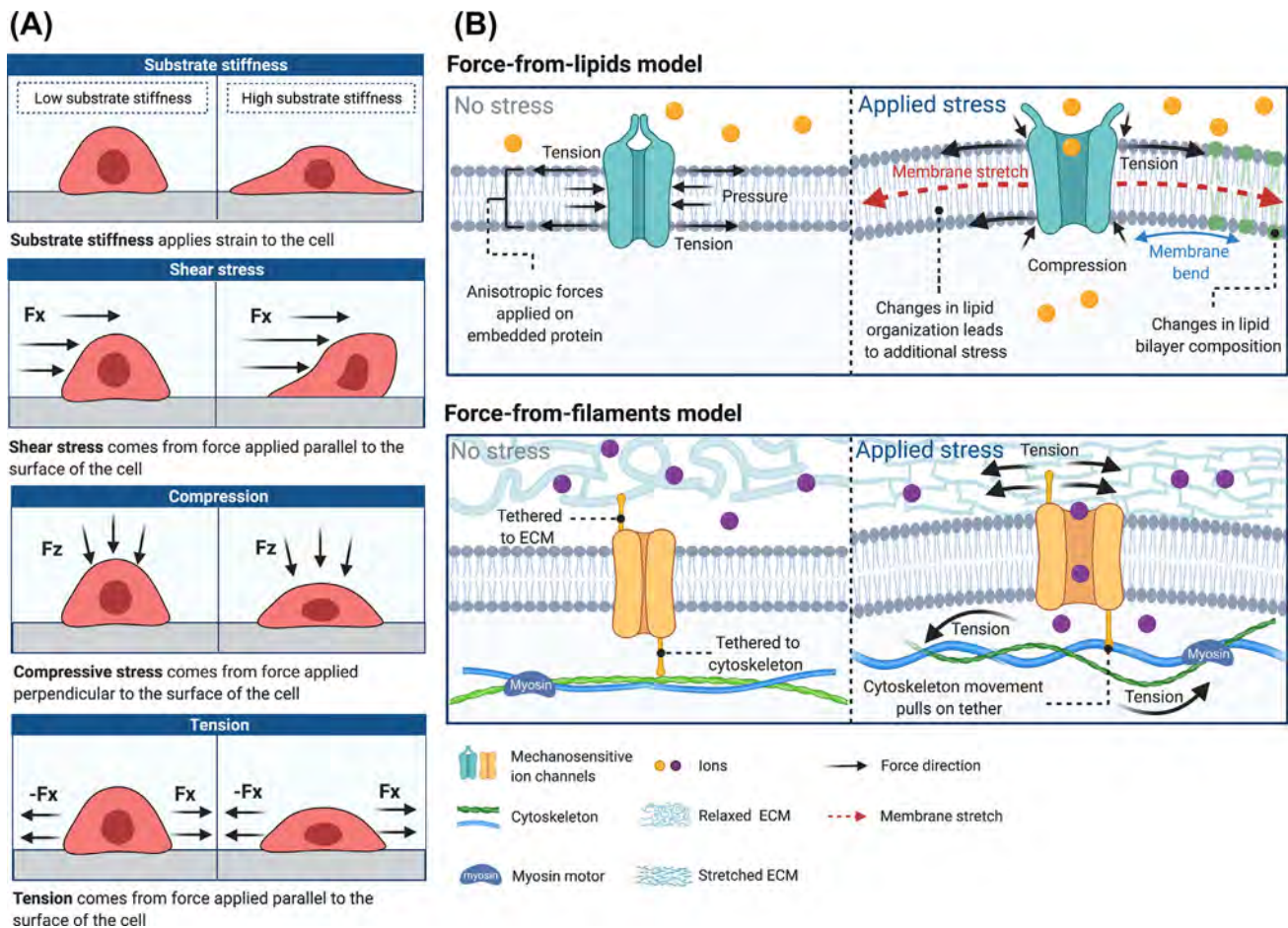
### Fluid Shear Stress in Brain Cancer

Due to aberrant angiogenic signaling and nonsynchronous formation of blood vessels, the vasculature and blood flow are heterogenous in brain tumors. Compared with nontumoral brain regions, gliomas contain more capillaries with larger diameter and slower blood flow [23], indicating that tumor endothelial cells are subjected to subphysiological shear stress. The **blood-tumor**

**Tumor cell hierarchy:** heterogeneous tumor cell populations, including cancer stem cells, progenitors, and differentiated cells, which create an ecosystem to regulate malignant growth.

**Viscoelastic:** description of the mechanical property of a material that displays both viscous and elastic qualities when subject to force. When deformed, the viscoelastic material simultaneously stores and dissipates energy.

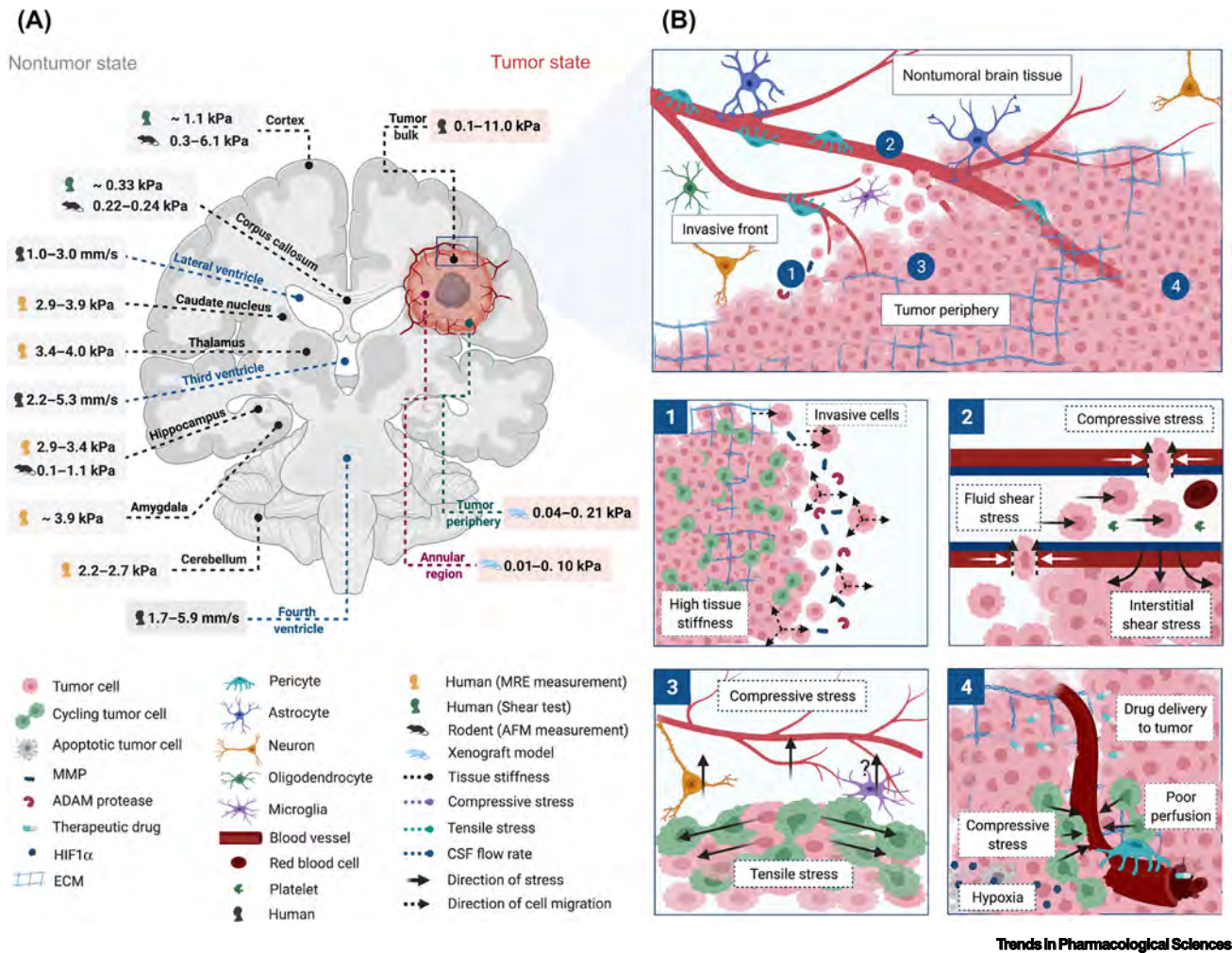
**Viscosity:** mechanical property of fluid that exhibits resistance to shear stress. When the material is subjected to shear stress, viscosity describes the energy dissipation of the material.



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Figure 1. Cells Can Perceive Mechanical Cues through Mechanosensitive (MS) Ion Channels. (A) Through cell-intrinsic and cell-microenvironment interactions, cells sense tissue mechanical properties, such as stiffness, and mechanical forces, including compression, tension, and shear stress. (B) Two gating mechanisms have been described for MS ion channels. The force-from-lipids model suggests that membrane-bound MS ion channels are subjected to anisotropic push and pull in the lipid bilayer. Changes in tension or stretching of the lipid bilayer in response to mechanical stimuli induce conformational changes to open the channel. The force-from-filament model suggests that MS ion channels are tethered to extracellular proteins or the cytoskeleton. Force-induced displacement of these tethers opens the channel.





**Figure 2. Malignant Transformation Disrupts the Brain Mechanical Optimum and Exposes Cells to Altered Mechanical Cues.** (A) The brain constructs a spatial and temporal mechanical optimum. Mechanical properties (e.g., tissue stiffness) and mechanical forces (e.g., shear stress) are heterogeneous in mouse, rat, and human brain [32]. Malignant transformation disrupts mechanical homeostasis, resulting in altered tissue stiffness, compressive stress, tensile stress, and shear stress in the brain. (B) Mechanical heterogeneity in tumors exerts microenvironmental effects: (1) elevated tumor stiffness promotes cell proliferation and invasiveness; (2) vascular remodeling influences the hematogenous spread of tumor cells. Tumor cells experience compressive stress during intravasation and extravasation. Circulating tumor cells are subjected to laminar or turbulent blood shear stress. Interstitial fluid originating from the leaky tumor vasculature applies shear stress to cells within tumor; (3) solid tumors can develop high tensile stress at the periphery and high compressive stress near the core. Tumor growth can apply compressive stress to surrounding tissue, causing nontumoral tissue displacement, neuronal cell death, vasculature impairment, and tumor cell infiltration; and (4) proliferating tumor cells apply compressive stress to the vasculature, which can result in poor perfusion of oxygen, nutrients, and therapeutic drugs. Low local oxygenation can further activate hypoxia-related signaling to impact tumor progression. Abbreviations: AFM, atomic force microscopy; CSF, cerebral spinal fluid; ECM, extracellular matrix; HIF, hypoxia-inducible factor; MMP, matrix metalloproteinase; MRE, magnetic resonance elastography

**barrier (BTB)**, the barrier formed by the BBB and its interacting cancer cells, displays abnormally increased permeability. Given that shear stress regulates endothelial tight junctions and their proliferation, subphysiological shear stress may contribute to the leaky BTB phenotype. Precise *in vitro* modeling and *in vivo* approaches are necessary to elucidate the role of shear stress in controlling the structures and functions of BBB and BTB. Tumor cell entry into the systemic circulation (**intravasation**), such as blood and CSF systems, and exit from them (**extravasation**) are necessary steps for metastasis. Primary brain tumors, such as medulloblastoma (MB, the most common pediatric malignant brain tumor) [24] and brain metastases, utilize blood and CSF flow for malignant dissemination. In zebrafish, circulating tumor cells (CTC) in blood arrest and

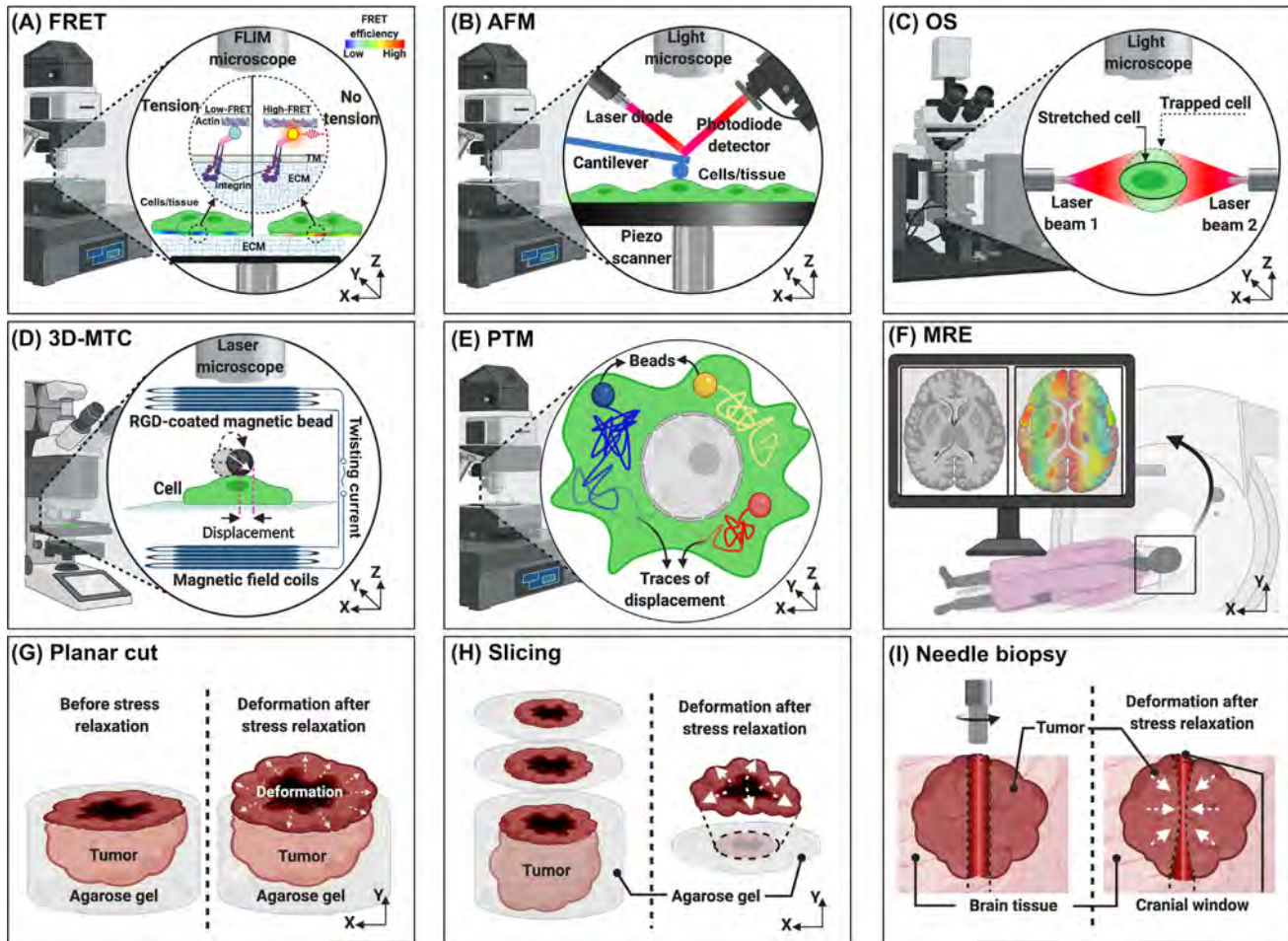
extravasate at an optimal level of shear stress [25]. Blood shear stress enriches metastatic cells with high expression of adhesion molecules, such as CD44 and ITGB3, to facilitate stable adhesion, extravasation, and metastasis [26] (Figure 2). Additionally, blood shear stress regulates the interaction between CTCs and neutrophils, platelets, and monocytes to further influence metastatic success [27].

CSF dynamics are altered in brain cancer. Heightened CSF pressure and hydrocephalus are frequently observed in brain tumors, such as GBM and MB, the growth of which can obstruct the CSF conduit pathway in brain ventricles. CSF is a mostly acellular environment, which is deprived of nutrients and growth factors. Metastatic cancer cells within CSF upregulate complement component 3 to disrupt choroid plexus epithelium and facilitate the entry of mitogens from blood to CSF to promote tumor growth [28]. CSF-borne cancer cells express iron-binding protein lipocalin-2 (LCN2) and its receptor SLC22A17 to harvest iron to support tumor growth in the leptomeningeal space [29]. Tumor cell presence in CSF is a prognostic factor for poor patient outcome. Furthermore, alterations in angiogenesis and vascular permeabilization also perturb ISF pressure and flow. Phase-contrast MRI of human gliomas showed that the ISF flow rate is heterogeneously increased compared with nontumoral brain [30]. While the role of blood shear stress in tumor has been extensively studied, how CSF-contacting tumor cells (e.g., tumor cells in brain ventricles, spinal canal, and the leptomeningeal spaces) or ISF-contacting tumor cells sense and respond to shear stress is largely unknown. Designing experimental platforms to model the unique flow rate, pattern, geometry, **rheology**, and liquid compositions of the CSF and ISF systems will reveal how biofluidic mechanics regulate tumor cell behaviors in the brain.

### Stiffness in the Brain

Tissue stiffness (Figure 1) is determined by mechanical properties of its extracellular, cellular, and biofluidic constituents. While the brain generally develops lower stiffness than other organs, spatial and temporal stiffness heterogeneities are detected [31–34] (Figure 2). For example, stiffness within rat dentate gyrus exhibited locoregional differences as determined by atomic force microscopy (AFM) (Figure 3 and Table 1). While the subgranular zone, which contains progenitor cells, and hilus, which receives axonal input, display similar stiffness (~50 Pa), the granule cell layer, where newly born neurons migrate, is twofold stiffer ( $111 \pm 18$  Pa). Microscale locoregional stiffness variations may influence cell fate specification and axon pathfinding [35]. Indeed, the role of tissue stiffness in brain cell types is manifold [36–38]. Neural stem cell (NSC) proliferation and differentiation are sensitive to tissue stiffness. Culturing adult NSCs on soft substrate (0.1–0.7 kPa) promoted neuronal differentiation, while oligodendrocyte differentiation was enhanced on stiff substrates (>7 kPa). Substrates with intermediate stiffness (3.5 kPa) induced maximal proliferation [39]. Another study reported that NSC proliferation increased on 0.1 kPa substrate, while 0.5 kPa and stiffer substrates (1–10 kPa) promoted neuronal and glial differentiation, respectively [40]. Interestingly, while adult NSCs cultured on 0.7 kPa substrate displayed pan-neuronal gene expression, changing substrate stiffness did not appear to alter neuronal subtype differentiation [41]. Molecularly, ECM-derived mechanical signals activate RhoA and Cdc42, increase NSC stiffness, and suppress neurogenesis *in vitro*. RhoA activation in hippocampal progenitors suppressed neurogenesis in adult rat hippocampus [42]. A stiff substrate increased MS ion channel PIEZO1 activity, which regulates the nuclear localization of Yes-associate protein (YAP), to promote neurogenesis and suppress gliogenesis [43]. In mouse embryonic cerebral cortex, the ventricular zone (VZ), subventricular zone (SVZ), and intermediate zone (IZ) harbor low, median, and high stiffness, respectively [31]. Since NSCs reside in VZ and migrate towards SVZ and IZ as they differentiate, these data provide physiological correlates for prior *in vitro* studies. Tissue stiffness also regulates axon growth and neurite extension. In *Xenopus*, a high-to-low stiffness gradient guides retinal ganglion cell axon growth along the optic tract toward the optic tectum [44] (Figure 4). In mouse hippocampal neurons,





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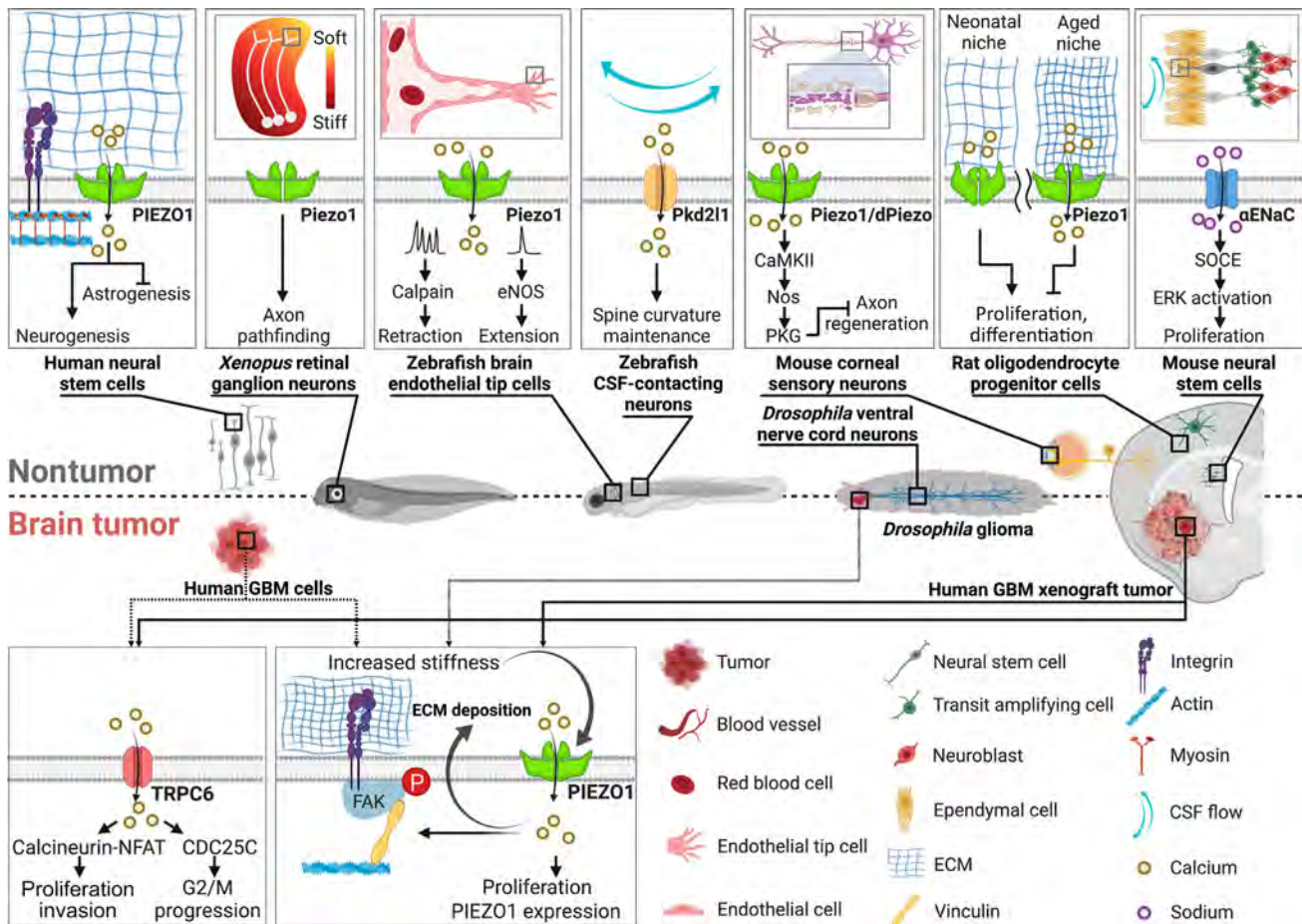
**Figure 3. Methods for the Quantitative Measurement of Cell/Tissue Mechanical Properties.** (A) Fluorescence resonance energy transfer (FRET) operates based on proximity-dependent energy transfer between two chromophore-labeled molecules (donor and acceptor; the FRET pair). Mechanical force (tension) changes the distance between the FRET pair and their fluorescence dynamics. In a relaxed state (no tension), the FRET pair is close enough for the donor to transfer energy to the acceptor, resulting in a high FRET signal. Mechanical tension on the FRET pair increases the distance between the donor and acceptor, which reduces energy transfer efficiency and results in a low FRET signal. (B) Atomic force microscopy (AFM) uses a cantilever to indent, scan, or tap an object. The deformed cantilever alters the laser path reflected into the photodiode detector to enable high-resolution measurement of mechanical properties and topography of the object. (C) Optical stretcher (OS), which uses laser power to trap and stretch cells in suspension, can be used for contact-free rheology measurements. (D) 3D magnetic twisting cytometry (3D-MTC) applies magnetic field-induced local mechanical force to live cells. Arginine-glycine-aspartic acid (RGD)-coated ferromagnetic beads are bound to the cell surface through receptors (e.g., Integrin). A twisting magnetic field applies mechanical torque in a specified direction on the cell surface. 3D-MTC can be combined with confocal microscopy for simultaneous force application and imaging. (E) Particle tracking microrheology (PTM) traces the motion of nanoparticles injected into live cells. PTM can be used to examine the viscoelastic properties of cells. (F) Magnetic resonance elastography (MRE) couples low-frequency vibrations with magnetic resonance imaging (MRI) to map tissue stiffness. (G) The planar cut method can be used to study the solid stress of a tissue in 2D. A tissue in agarose gel is cut along the X–Y axis. The cut releases solid stress, which allows the tissue that previously experienced compression and tension to expand and shrink, respectively. The extent of tissue deformation informs the solid stress and elastic energy of the tumor (H) The slicing method is based on the same principle as the planar cut method. A tissue is sliced to release solid stress and reveal the solid stress and elastic energy of the tissue at multiple planes. (I) The needle biopsy method uses needle insertion to extract a tissue piece. The subsequent 3D deformation of the vacant space can be used to quantify the locoregional solid stress and elastic energy of the tumor.

high stiffness inhibits neurite growth by regulating receptor-like protein tyrosine phosphatase  $\alpha$  (RPTP $\alpha$ ), which complexes with  $\alpha 5\beta 6$  integrin at the leading edge to suppress axon extension [45]. By contrast, high stiffness promotes neurite growth and branching of mouse cortical neurons [46]. These data suggest that spatiotemporally heterogeneous stiffness serves as a mechanical blueprint to instruct the behaviors of NSCs, progenitors, neurons, and glia.

Table 1. Common Methods to Measure Biomechanical Properties of Cells and Tissues

Device	Target	<i>In vitro/in vivo</i>	Measurement	Dimension	Figure in main text	Refs
Fluorescence resonance energy transfer (FRET)-based force/tension sensors						
Fluorescence lifetime, acceptor photobleaching, sensitized emission	Whole animal; live tissue; cells; subcellular structure; structural molecule	<i>In vitro; in vivo</i>	Tension on ECM, cellular, and subcellular structures	2D; 3D	3A	[108]
Force spectroscopy						
Atomic force microscopy (AFM)	Tissue; cell; subcellular structure	<i>in vitro</i>	Cell adhesion; stiffness; topological, electrical and magnetic properties, thermal conductivity	2D; 3D	3B	[109,110]
Optical tweezers	Cell; organelle; intracellular motor; DNA strand	<i>in vitro</i>	Cell adhesion; stiffness; DNA uncoiled force	2D; 3D	–	[109,110]
Dual-beam optical stretcher (OS)	Suspended cell; organelle; phospholipid; vesicle; membrane	<i>in vitro</i>	Cell adhesion; viscoelasticity; stiffness; refraction index; cell size	2D; 3D	3C	[109,111]
Magnetic tweezer	Cell; organelle; intracellular motor; DNA strand	<i>in vitro</i>	Cell adhesion; rheological properties; viscoelasticity; Stiffness; DNA uncoiled force	2D; 3D	–	[110]
3D-magnetic twisting cytometry (3D-MTC)	Cell; organelle; subcellular structure	<i>In vitro; in vivo</i>	Cell adhesion; rheological properties; viscoelasticity; stiffness; shear modulus of membrane; DNA uncoiled force	2D; 3D	3D	[109,112]
Rheology						
Particle-tracking microrheology (PTM)	Cytoplasm; biofluid	<i>In vitro; in vivo</i>	Intracellular rheology; viscoelasticity; viscosity	2D; 3D	3E	[109,113]
Parallel plate rheometer (PPR)	Tissue; cell; biofluid	<i>In vitro</i>	Viscoelasticity; viscosity; stiffness; shear modulus; fracture and yield strength	2D, 3D	–	[109]
Solid stress mapping						
Planar cut	Tissue	<i>In vitro</i>	Solid stress mapping; elastic energy	2D; 3D	3G	[14]
Slicing	Tissue	<i>In vitro</i>	Solid stress mapping; elastic energy	2D	3H	[14]
Needle biopsy	Tissue	<i>In vitro; in vivo</i>	Solid stress; elastic energy	1D	3I	[14]
Oil droplet	Tissue	<i>In vivo</i>	Solid stress	3D	–	[114]
Elastography						
Magnetic resonance elastography (MRE)	Organ; tissue	<i>In vitro; in vivo</i>	Stiffness mapping of soft tissue	3D	3F	[115]
Ultrasound electrography	Organ; tissue	<i>In vitro; in vivo</i>	Stiffness mapping of soft tissue	3D	–	[115]

Aging is associated with a decline in cognitive abilities and neuroplasticity, and age-dependent changes in brain mechanical properties have been reported. Tissue stiffness of rat cortex and hippocampus also displays changes during aging [34]. The microenvironment of oligodendrocyte progenitor cells (OPCs) stiffens during aging, with increased stiffness reducing the proliferative capacity of OPCs. Interestingly, culturing aged OPCs under stiffness comparable with that of neonatal OPC microenvironment rejuvenated the proliferation and differentiation abilities of aged OPCs [47] (Figure 4). Magnetic resonance elastography (MRE) and AFM studies (Figure 3 and Table 1) showed that the stiffness of multiple brain regions, including hippocampus,



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**Figure 4. Mechanosensitive (MS) Ion Channel Functions in the Nervous System and Brain Cancer.** Top panels: PIEZO1 senses increased stiffness to promote neurogenesis and inhibit astrogenesis of human neural stem cells (NSCs) *in vitro*. In developing *Xenopus*, Piezo1 mediates axon pathfinding of retinal ganglion neurons down a microenvironmental stiffness gradient. In zebrafish larvae, Piezo1 regulates calcium transient frequencies in endothelial tip cells to facilitate vascular pathfinding in the brain. High calcium transient frequencies lead to branch retraction through calpain, whereas low calcium transient frequencies lead to branch extension through endothelial nitric oxide synthase (eNOS). Pkd211 senses cerebrospinal fluid (CSF) flow in CSF-contacting neurons to facilitate the maintenance of proper spine curvature. In mouse corneal sensory neurons and *Drosophila* ventral nerve cord neurons, Piezo1 and dPiezo inhibit axon regeneration after injury through calcium/calmodulin-dependent kinase II (CaMKII), NOS, and cGMP-dependent protein kinase (PKG), respectively. As rat brain stiffness increases with age, oligodendrocyte precursor cells sense microenvironmental stiffness through Piezo1 to reduce proliferation and differentiation. Subependymal zone NSCs of adult mice express the epithelial sodium channel (ENaC), which senses CSF flow to induce sodium influx and membrane depolarization. Subsequent store-operated calcium entry (SOCE) leads to extracellular signal-regulated kinase (ERK) activation and cell proliferation. Bottom panels: Glioblastoma (GBM) cells express Transient receptor potential cation channel 6 (TRPC6), which enhances proliferation and motility *in vitro* via calcium-calcineurin-nuclear factor of activated T cells (NFAT) signaling. TRPC6 regulates G2/M progression of GBM cells through cell division cycle 25 homolog C (CDC25C). PIEZO1 senses increased tissue stiffness to induce localized calcium influx at focal adhesions and promote extracellular matrix (ECM) remodeling, integrin signaling, proliferation, and its own expression to form a feedforward loop that aggravates GBM malignancy.

cerebrum as well as the frontal, occipital, parietal, and temporal lobes, increased during aging in humans, mice, and rats [33,34]. These data raise an important question: is the increase in microenvironmental stiffness a mechanical hallmark of brain aging? If so, modulating tissue stiffness or stiffness sensors may offer therapeutic opportunities to alleviate aging-associated symptoms.

### Stiffness in Brain Cancer

Brain tumors profoundly remodel their ECM compared with nontumoral brain. Tenascin-C (TNC), which displays high expression in the developing brain, is upregulated in GBM and ependymoma



[16,48,49]. High expression of hyaluronic acid, collagen, laminin, brevican, and ECM crosslinking proteins are reported in gliomas and MB [16,49–51]. Gliomas in patient samples demonstrate stiffness increases from low (0.05 kPa) to high (13 kPa) tumor grade in a TNC-dependent manner [16]. MBs display alterations in protein and lipid contents of the ECM and stiffness ranging from 1.9 to kPa 75.7 kPa as determined by Raman spectroscopy and atomic force microscopy [52]. Additionally, meningioma develops intra- and intertumor stiffness heterogeneity (2–10 kPa) [53]. These findings demonstrate a role for elevated ECM proteins to mechanically strengthen brain tumors with spatiotemporal variabilities (Figure 2). In addition to ECM, cell proliferation within a confined space, infiltration of immune and stromal cells, and ISF and blood flow collectively contribute to altered tissue stiffness in brain tumors [10,11,17,18]. Tissue stiffness influences tumor cell morphology, proliferation, and migration. While human GBM cells cultured on stiff substrates (119–>1000 kPa) were well spread with overt actin stress fibers and focal adhesions, they appeared rounded and developed less focal adhesions under low stiffness conditions (0.08–0.8 kPa) [54]. High stiffness increased GBM cell proliferation, lamellipodia-based cell motility, and epidermal growth factor receptor (EGFR) localization and activation at focal adhesions [55], implicating stiffness-dependent EGFR signaling in the pathogenesis of GBM. Whether stiffness regulates other growth-promoting signaling pathways in brain tumors remains to be determined.

While tumors generally develop increased tissue stiffness compared with their normal tissue counterparts, intertumoral, intratumoral, and temporal stiffness heterogeneities will likely arise. Supporting this notion, elastography studies showed that certain GBM regions can be softer than nontumoral brain tissues [56,57]. We suggest that distinct **mechanical niches** and stiffness optimums govern behaviors of cell types within the **tumor cell hierarchy**. Defining such niches may reveal opportunities to suppress malignant growth. Furthermore, revealing the mechanical properties of tumor cell-of-origin should bring forward insights into how cell mechanics cooperates with genetic mutations to influence oncogenesis and **cancer evolution**. For example, GBM occurrence is higher and survival is shorter in the elderly population. Does brain stiffening that occurs during aging contribute to increased incidence and aggressiveness of GBM? Figure 3 and Table 1 describe common methods to measure biomechanical properties of cells and tissues.

### Mechanosensitive Ion Channels

Ion channels sense diverse physicochemical stimulations to control ion flux across membranes. MS ion channels perceive mechanical cues (e.g., solid stress, fluid shear stress, and microenvironmental stiffness) to permeate ions for intracellular electrical and biochemical signaling. Two gating mechanisms have been described [58]. First, the force-from-lipids model suggests that force on membrane lipids induces a conformational change to open the channel. Second, the force-from-filament model suggests that the cytoskeleton or ECM proteins connect to MS ion channels, and the force-induced displacement of such tethers opens the channel (Figure 1B). As early as 1984, mechanically activated ionic currents were recorded from embryonic chick skeletal muscle cells [59]. Ten years later, the first MS ion channel, MscL, was cloned from bacteria [60]. The past decades have seen a boom in the identification and functional characterization of MS ion channels. Taking MS ion channels in the nervous system as an example (Figure 4), PIEZO1 senses increased stiffness to promote neurogenesis and inhibit astrogenesis of human neural stem cells *in vitro* [43]. In *Xenopus*, Piezo1 mediates axon pathfinding of retinal ganglion neurons along a tissue stiffness gradient [44]. In zebrafish, it regulates calcium influx frequency in brain endothelial tip cells to facilitate vascular pathfinding. High frequencies lead to branch retraction through calpain, while low frequencies lead to branch extension through endothelial nitric oxide (eNOS) signaling [61]. As brain stiffness increases with age, rat OPCs sense stiffness through Piezo1 to reduce their proliferation and differentiation potential in aged brain [47].

Subependymal zone NSCs of adult mice express the epithelial sodium channel ENaC, which senses CSF shear stress to induce sodium influx, leading to extracellular signal-regulated kinase (ERK) activation and cell proliferation [62]. Cationic channel Pkd2l1 senses flow in CSF-contacting neurons to regulate zebrafish spine curvature [63]. In *Drosophila* ventral nerve cord neurons and mouse corneal sensory neurons, Piezo inhibits postinjury axon regeneration through calcium/calmodulin-dependent kinase II, NOS, and cGMP-dependent protein kinase (PKG) [64]. Indeed, MS ion channels mediate physiological processes, such as touch, pain, proprioception, hearing, breathing, developmental processes such as vascular and lymphatic system patterning, and pathological conditions such as deafness, xerocytosis, scoliosis, respiratory distress, and muscular atrophy. We direct readers to excellent reviews on these topics [58,65].

### MS Ion Channels in Cancer

As illustrated earlier, pervasive solid stress and fluid shear stress are present in solid tumors, which develop profound alterations of tissue stiffness. Given that each cell can be considered a MS unit, the cell nucleus and intracellular organelles, which are enclosed by semipermeable membranes, can also be equipped with MS ion channels to sense and respond to mechanical cues. Through the LINC complex, **nuclear actin** and the **nucleoskeleton** are mechanically coupled with the cytosolic actin cytoskeleton to mediate force transmission between the cytosol and nucleus. Furthermore, **viscoelastic** cytoplasm and nucleoplasm allow force transmission among intracellular materials. MS ion channels are prime 'molecular bridges' to mediate mechanically activated communications on both inter- and intracellular scales (Box 1). Here, we discuss MS ion channels in cancer of the brain and other origins.

### Piezo Channels

Piezos are calcium-permeable cationic channels that can be activated by solid and fluid shear stress. The evolutionarily conserved mechanotransduction functions of Piezos have been

#### Box 1. Cellular Mechanics and MS Ion Channels

##### Plasma Membrane

- The plasma membrane, which is considered incompressible, displays topological restructuring, including bending, folding, and changes in curvature.
- By changing the level and distribution of phospholipids and cholesterol, the plasma membrane develops dynamic stiffness, fluidity, and **viscosity**.
- The force-from-lipids model suggests that force-induced plasma membrane deformation causes lipid layer mismatch and alters mechanical strains to activate MS ion channels.
- The force-from-filaments model suggests that activation of MS ion channels occurs through a disturbance in the ECM or cytoskeleton that the channels are physically tethered to.

##### Cytoplasm

- The cytoskeleton bridges plasma and nuclear membranes, permitting outside-in and inside-out transmission of mechanical signals among the ECM, cytosol, and nucleus.
- Intracellular organelles experience forces from soluble (e.g., cytosol) and insoluble (e.g., cytoskeleton, contacting organelles) constituents.
- MS ion channels on intracellular organelles remain unidentified.

##### Nucleus

- The nucleus is a MS structure that responds to mechanical stress and ECM stiffness.
- Nuclear stiffness is determined by the mechanical properties and organizations of the nuclear envelope, Lamins and Lamin-associated proteins, nuclear matrix, and chromatin.
- Nuclear mechanics regulate chromosome territories, topologically associating domains, chromatin loops, chromatin (de)condensation, and accessibility.
- A decrease in nuclear stiffness facilitates cancer cell migration and creates an open-chromatin state for DNA repair.
- MS ion channels on the nuclear membrane remain unidentified.

demonstrated from major model organisms, including *Arabidopsis*, *Caenorhabditis elegans*, *Drosophila*, *Xenopus*, zebrafish, mouse, and human. In gastric cancer cell lines, PIEZO1 promotes cell proliferation and migration [66,67]. It also mediates MS ion channel activity and regulates cell motility in a breast cancer cell line, and high PIEZO1 expression correlates with poor survival in patients with breast cancer [68]. In a brain metastatic breast cancer cell line, PIEZO2 perceives substrate stiffness to regulate calcium entry and RhoA activity to promote the formation of stress fibers and focal adhesions, and knockdown of PIEZO2 suppresses the motility and matrix-degrading ability of these cells [69]. In human gliomas, high PIEZO1 expression associates with multiple biomarkers (e.g., IDH wild-type, non-1q/19q co-deletion, and non-G-CIMP phenotype) of poor prognosis and predicts worse patient outcome. In *Drosophila*, Piezo promotes mitosis and tissue stiffening of gliomas, while its function is dispensable for nontransformed brains. PIEZO1 confers mechanosensitivity to human GBM stem cells, and PIEZO1 knockdown suppresses xenograft GBM growth and prolongs mouse survival. In these cells, PIEZO1 localizes at focal adhesions to activate integrin-FAK signaling, regulate ECM production, and reinforce tissue stiffening. In turn, a stiffer microenvironment elevates PIEZO1 expression. Thus, targeting PIEZO1 represents a strategy to break a reciprocal, disease-aggravating feedforward circuit between tumor cell mechanotransduction and tissue mechanics [51] (Figure 4). Importantly, PIEZO channels are highly expressed in human malignancies, suggesting that PIEZO-mediated mechanotransduction is a general mechanism used by tumors [51,70].

#### TRP Channels

Transient receptor potential (TRP) proteins are cationic channels that can be activated by physicochemical stimulations to regulate diverse sensory functions, such as taste, vision, hearing, touch, pain, and proprioception [71]. Several TRP channels are implicated in malignancies. TRPM7, a calcium- and magnesium-permeable channel, is required in GBM cells for the activation of Notch and JAK/STAT3 pathways to increase expression of the cancer stem cell marker ALDH1. TRPM7 silencing reduces the proliferation, survival, and invasion of GBM cells [72]. Aberrantly elevated JAK/STAT3 signaling activity is estimated to occur in >70% of human cancers [73]. Constitutively active STAT3 confers anchorage-independent growth and tumorigenic capacity to fibroblasts [74]. Given that TRPM7 function has been implicated in multiple cancer types, an interesting open question is whether activation of JAK/STAT3 signaling is a common downstream effect of TRPM7 in tumorigenesis.

Both TRPC1 and TRPC6 mediate intracellular calcium increase induced by platelet-derived growth factor (PDGF). TRPC1 is required for PDGF-dependent calcium influx and chemotaxis (directed migration) of a GBM cell line. In response to PDGF, intracellular TRPC1 translocates to lamellipodia at the leading edge of migrating GBM cells [75]. Similarly, PDGF promotes calcium permeation through TRPC6 to enhance GBM cell growth and invasion *in vitro* by activating the calcineurin-nuclear factor of activated T-cell (NFAT) pathway [76]. Furthermore, loss of TRPC6 induces G2/M phase cell cycle arrest and suppresses GBM growth in xenograft mouse models [77] (Figure 4). Of note, TRPC6 expression is augmented by hypoxia, which could drive aggressive and malignant states in GBM. Another interesting observation is that inhibition of TRPC6 or NFAT pathway activation results in reduced angiogenic ability of conditioned medium from GBM cells, suggesting that TRPC6 function in hypoxic tumor cells induces vascularization through paracrine signaling [76].

Another TRP member is TRPV4, the expression of which is associated with poor survival of patients with breast, gastric, and ovarian cancers [78], implicating a role of TRPV4 in epithelial cancers. Trpv4 knockdown resulted in a reduction in the number, but not the size, of metastatic nodules in a mouse allograft model of metastatic breast tumors, consistent with the observation



Table 2. MS Ion Channels in Cancer<sup>a</sup>

MS ion channel	Function in nontumor tissues			Function in tumor		Pharmacological targets	
	Ionic selectivity	Cell type/tissue	Type of stimulation	Function	Cancer type		Function in cancer
PIEZO1	Nonselective Ca <sup>2+</sup> -permeable cation channels	Vascular endothelium; lung macrophages; corneal sensory nerves; neural stem cells; lymphatic endothelium; epithelial cells	Hematomous shear stress; cyclical hydrostatic pressure; substrate stiffness-dependent traction force; mechanical stretch	Angiogenesis and vascular maturation [116] Arterial blood pressure regulation [117] Initiation of inflammatory response by EDN-1 transcription [118] HIF1 $\alpha$ stabilization [118] Inhibition of axon regeneration [64] Neuronal–glial lineage choice: activation promotes neuronal differentiation [43] Lymphatic valve development [119] Rapid proliferation [120] Brain vascular pathfinding [61]	Glioblastoma [51] Breast cancer [68] Gastric cancer [67] Bladder carcinoma [70] Osteosarcoma [70] Synovial sarcoma [70] Colon cancer [121]	Cell proliferation [67] [51] Cytoskeleton remodeling [51] ECM remodeling and tissue stiffness [51] Stress fiber polymerization [51] Cell migration [67] [121] Cell viability [70] Metastasis, HIF1 $\alpha$ , and VEGF expression [121]	Yoda-1 (agonist), specific to Piezo1 [96] Jedi1/2 (agonist), specific to Piezo1 [98]
PIEZO2	Nonselective Ca <sup>2+</sup> -permeable cation channels	Dorsal root ganglion proprioceptive neurons; caudal sensory neurons; vagal sensory neurons	Static compressive force; membrane indentation; respiratory airway stretch; membrane indentation	Innocuous touch somatosensation [122] Proprioception [123] Noxious touch somatosensation [124] Required for proper respiratory control [125]	Glioma [70] Breast cancer [69]	Angiogenesis via tumor endothelial cell proliferation [70] Tube formation [70] Invasion [69]	–
OSCs (TMEM63s)	Non-selective cation channels with some chloride permeability	–	–	–	–	–	–
ENaC (SCNN1A)	Na <sup>+</sup>	Subependymal zone neural stem cells	Cerebrospinal fluid shear stress	Adult neurogenesis [62]	Glioma [91] Hepatocellular carcinoma [126]	Cell volume (ASIC1) [91] Cell proliferation [91] Cell migration [91] Metastasis (ASIC2) [91]	S3969, high efficacy in activating hENaC [127]
TRPC1	Nonselective Ca <sup>2+</sup> -permeable cation channels	Neuronal growth cones	Substrate stiffness	Axon guidance [60]	Glioma [75]	Platelet-derived growth factor (PDGF)-induced chemotaxis [75]	–

TRP Channel	Nonselective Ca <sup>2+</sup> -permeable cation channels	Endocardial cells	Mechanical stretch	Endocardial/myocardial crosstalk [128]	Gloma [76,77]	Migration [76] Invasion [76] Angiogenesis [76] Regulates notch pathway [76] Regulates calcineurin-NFAT pathway [76] Stabilizes HIF-1 $\alpha$ [129] Glucose uptake [129] Vascular branching [129] G2/M transition [77]	-
TRPM7	Nonselective Ca <sup>2+</sup> -permeable cation channels	-	-	-	Gloma [72] Lung cancer [70]	Cell proliferation [72] Prosurvival [72] Glioma stem cell maintenance [72] Cell migration [70]	-
TRPV4	Nonselective Ca <sup>2+</sup> -permeable cation channels	Dorsal root ganglion sensory neurons; bladder urothelial cells	Tail pressure; mechanical stretch	Noxious touch somatosensation [130]	Breast cancer [70] Gastric cancer [70] Renal cancer [70]	Endothelial cell migration [70] ECM breakdown [70] EMT/MET [70] Cell migration [70] E-cadherin expression [70] Invadopodia formation [70] Increased cell deformability [70]	GSK1016790A (agonist), specific to TRPV4 [131] GSK2193874 (antagonist), specific to TRPV4 [132]
TRPP3 (PKD2L1)	Nonselective Ca <sup>2+</sup> -permeable cation channels	CSF-contacting neurons	Membrane indentation	Maintenance of spine curvature [63]	-	-	-
TREK-1	K <sup>+</sup>	Dorsal root ganglion sensory neurons	-	Regulator of innocuous and noxious somatosensation [58]	Prostate [70,79] Ovarian [70] Bladder [70] PDAC [70]	Cell proliferation [70,87] G1/S cell cycle progression [70] Migration [70]	Spadin (antagonist) [133]
TREK-2	K <sup>+</sup>	Dorsal root ganglion nociceptive neurons	-	Mechanical and osmotic pain somatosensation [134]	Bladder [88]	G1/S cell cycle progression [88]	-

<sup>a</sup>While these ion channels have many functions in healthy tissues, this table highlights studies that indicate their physiological roles in the nervous system. Only channels discussed in the main text are included.

that TRPV4 function is required for cell migration but not proliferation of human breast cancer cells. In addition, TRPV4 overexpression could remodel actin cytoskeleton to decrease cell stiffness. These observations raise the possibility that TRPV4 augments metastatic ability by enhancing cancer cell deformability to facilitate traveling through physically confining spaces *in vivo* [78].

TRP channels are multimodal sensory molecules that respond to various types of stimulation, including, but not limited to, mechanical forces. The examples discussed earlier and Table 2 illustrate the involvement of TRP channels, as well as other potential MS ion channels, in human cancers. While several TRP channels, such as TRPM7 [79], TRPC1 [80], TRPC6 [81], and TRPV4 [82], have been considered as candidate MS ion channels, it remains to be established whether TRP channels regulate cancer cell behaviors through their mechanosensing ability.

### K<sub>2P</sub> Channels

Potassium channels, which form the largest ion channel family, can be divided into four classes based on their structure and activation mechanisms: voltage-gated potassium (K<sub>v</sub>) channels; calcium-activated potassium (K<sub>Ca</sub>) channels; inward rectifying potassium (Kir) channels; and two-pore domain potassium (K<sub>2P</sub>) channels. K<sub>2P</sub> channels are usually constitutively open as 'leak channels' to maintain negative resting membrane potential. Three K<sub>2P</sub> channels have been shown to be mechanically activated: TREK-1 [83], TREK-2 [84,85], and TRAAK [86]. TREK-1 is highly expressed in prostate cancer but not in normal prostate or benign prostatic hyperplasia. TREK-1 overexpression increases the proliferation of normal prostate epithelial cells, which can be reduced by a TREK-1 inhibitor or expression of dominant-negative TREK-1 [87]. In a bladder cancer cell line, mechanical stretch induced TREK-2-like currents, and knock-down of TREK2 reduced Cyclin D expression and induced G1/S phase cell cycle arrest [88]. It will be important to define the mechanism by which MS potassium channels regulate cancer cell behaviors and the *in vivo* role of these channels in tumor growth.

### ENaC/DEG Channels

First discovered as MS proteins to mediate touch and nociception in *C. elegans*, ENaC [epithelial sodium channel/degenerin (ENaC/DEG)] proteins are sodium-permeating, amiloride-sensitive channels mostly expressed in epithelial cells and the nervous system. ENaC/DEG channels display a spectrum of functions, such as epithelial sodium transport, salt taste, and sensory mechanotransduction [89,90]. Glioma cells undergo regulatory volume increase subsequent to cell shrinkage induced by hyperosmolar solutions. Acid-sensing ion channel 1 (ASIC1), a member of the ENaC/DEG channel family, mediates amiloride-sensitive currents in glioma cells and is required to restore cell volume in response to hyperosmolar stress [91]. This finding suggests that the ENaC channel controls tumor cell volume to facilitate cell division and/or cell migration. Supporting this notion, ASIC is required to conduct the inward sodium current that promotes glioma cell proliferation *in vitro* [92]. Dysregulated pH is a hallmark of cancer because tumor cells develop an increased and decreased intracellular and extracellular pH, respectively, compared with non-malignant cells [93]. These data raise the intriguing prospect that ASICs act as vital sensors to integrate pH and mechanical signals during oncogenic transformation and progression.

### Other MS Ion Channels

Recently, OSCA1.2, one of the OSCA proteins of flowering plant *Arabidopsis thaliana*, was shown to encode a pore-forming MS ion channel. OSCA/TMEM63 proteins are conserved across plants, flies, and mammals, suggesting that the OSCA family of proteins comprises the largest family of MS ion channels identified to date [94]. Investigating the role of the ever-expanding family of MS ion channels, such as OSCA proteins, in cancer will reveal mechanotransduction events in cancer and uncover how mechanical forces fuel malignant growth.



### Therapeutic Targeting of MS Ion Channels in Cancer

Ion channels are well recognized therapeutic targets for treating human diseases, such as neurological and cardiovascular disorders. Approximately 20% of US FDA-approved drugs have ion channels as their primary targets [95]. Applying mechanical stimulations on a large scale with high spatiotemporal resolution to screen for chemical modulators of MS ion channels has been technically challenging. As a result, pharmacological targeting of MS ion channels is in its infancy. While a growing list of MS ion channels has been implicated in cancer, most existing chemical modulators do not display sufficient specificity and lack *in vivo* validations (Table 2) [65]. Furthermore, certain modulators (e.g., PIEZO-specific antagonists), the discovery of which will be of tremendous scientific and clinical significance, remain unidentified. Ingenious experimental platforms have led to the identification of *bona fide* MS ion channels and receptors and several chemical modulators [96–98]. Accumulating insights into MS ion channel structures, gating mechanisms, and *in vivo* functions should facilitate the drug discovery process. Given that mechanosensation regulates various physiological processes, systemic inhibition of MS ion channels may result in undesired impacts. Locoregional modulation of MS ion channels in a spatiotemporally controlled manner may be the strategy to interfere the ability of the tumor to sense and respond to microenvironmental cues while minimizing treatment side effects.

### Concluding Remarks and Future Perspectives

Force generation, transmission, and perception shape all aspects of life. Loss of mechanical homeostasis is a physical trait of cancer. With the ability to convert mechanical cues into intracellular signaling in milliseconds, MS ion channels are prime molecules to investigate mechanotransduction mechanisms. In this review, we deconstructed brain mechanics at homeostasis and tumor states, illustrated examples of MS ion channel functions in cancer, and identified the potential of modulating MS ion channels to treat cancer. Myriad mechanical cues are present in a tumor. Future investigations are warranted to assign specific modes of force and mechanical signals that gate the functions of MS ion channels during malignant growth and progression. As the field of cancer mechanobiology develops, we anticipate advancements in chemical and mechanical modulators of MS ion channels. For example, high-throughput microfluidic platforms, which have proven useful in identifying novel mechanosensors (e.g., GPR68), may offer opportunities to screen chemical entities for drug discovery [97]. Emerging techniques, such as the use of hydrogels to regulate tissue mechanics [99] and noncontact long-range magnetic approaches to activate Piezo1 in freely behaving animals [100], support the future development of therapeutic modulations for MS ion channels.

The brain tumor microenvironment is a complex ecosystem that includes both tumor cells and nontumoral cell types, such as neurons, astrocytes, and endothelial and immune cells. Cell divisions, angiogenesis, cell infiltrations, and fluidic flows offer ample mechanical cues to all cell types within this ecosystem. How MS ion channels confer mechanosensitivity to cancer-associated cells to influence tumor progression is unexplored (see Outstanding Questions). Piezo1-mediated calcium influx strengthens actomyosin to optimize T cell activation [101]. Cultured microglia migrate toward areas with higher substrate stiffness [102]. Microenvironmental stiffness induces microglia polarization and TGF $\beta$ 1 expression to remodel retinal vasculature [103]. Endothelial cells sense shear stress and tissue stiffness to govern vascular patterning [19,61]. Furthermore, tumor cells (of glioma or brain metastases) form synapses with neurons. Presynaptic neurons release glutamate to activate NMDA and AMPA receptors expressed in postsynaptic tumor cells, and this synaptic transmission increases tumor cell proliferation and invasiveness, thereby reducing the survival of tumor-bearing mice [104–106]. Intriguingly, both force-from-lipids and force-from-filaments mechanisms have been implicated in the mechanosensory transduction of NMDAR [107]. Elucidating whether and how MS ion channels regulate mechanotransduction in T cells, microglia, endothelial cells, and tumor–neuron synapses may bring to light unexpected insights into how mechanical forces

### Outstanding Questions

Is mechanical heterogeneity (e.g., locoregional compression, tension, shear stress, and stiffness) a cancer hallmark?

Does mechanical heterogeneity regulate tumor initiation, progression, metastasis, or therapy response?

What functional roles do cardiac rhythm-induced cyclic compression and tension have in healthy and diseased (e.g., cancer) brains?

How does mechanical stress influence genetic mutations and cancer evolution? Does physical squeezing of the nuclear envelope during tumor cell intravasation and extravasation induce DNA damage to increase mutation burden and promote emergence of clones with elevated metastatic potential?

Do various tumor cell types (e.g., cancer stem cells, progenitors, or differentiated cells) reside in distinct ‘mechanical niches’, which favor the maintenance and expansion of each cell population?

Do tumor cells and tumor-associated cells (e.g., neurons, glia, and endothelial and immune cells) cooperate to establish geometrically distinct mechanical niches in the tumor?

Do mechanical cues regulate the choice of quiescence versus cell cycling of cancer stem cells?

How do force transmission and tissue stiffness regulate the interaction between tumor and nontumoral cell types (e.g., neurons, glia, endothelial cells, or immune cells) in the brain?

Does the growth of therapy-resistant and metastatic tumors depend on mechanical niches that are different from therapy-sensitive and primary tumors, respectively?

Are there MS ion channels on the nuclear membrane?

Do MS ion channels confer mechanosensitivity to the cell nucleus to regulate genome organization, chromatin accessibility, or gene expression?

orchestrate cellular architecture and signaling interplays among various cell types within the tumor ecosystem. We propose that investigating MS ion channels in cancer represents a new frontier to discover therapeutic opportunities by revealing novel mechano-electrical-chemical signaling mechanisms in cancer biology.

### Acknowledgments

We thank Chi-Chung Hui and Siyi Wanggou for critical reading and comments on the manuscript. This work is supported by SickKids Foundation, Arthur and Sonia Labatt Brain Tumour Research Centre, Garron Family Cancer Centre, b.r.a.i.n.child, Meagan's HUG, Natural Sciences and Engineering Research Council (NSERC) Discovery Grant, Ontario Institute for Cancer Research (OICR) Translational Research Initiative, Canadian Institute of Health Research (CIHR) Project Grants, Concern Foundation Conquer Cancer Now Award, EMHSEED program, Early Researcher Award, and Sontag Foundation Distinguished Scientist Award to X.H. A.M. is supported by an Ontario Graduate Scholarship. S.B. is supported by an International Postdoc Grant from Swedish Research Council (Vetenskapsrådet). X.C. is supported by SickKids Restracom Scholarship. X.H. is a Catalyst Scholar at The Hospital for Sick Children and Canada Research Chair in Cancer Biophysics, and is grateful for the love and support of Lucas and Liam Huang.

### Declaration of Interests

The authors declare no conflict of interests.

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