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Review article

Research progress on the regulatory role of cell membrane surface tension in cell behavior

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ABSTRACT

Cell membrane surface tension has emerged as a pivotal biophysical factor governing cell behavior and fate. This review systematically delineates recent advances in techniques for cell membrane surface tension quantification, mechanosensing mechanisms, and regulatory roles of cell membrane surface tension in modulating major cellular processes. Micropipette aspiration, tether pulling, and newly developed fluorescent probes enable the measurement of cell membrane surface tension with spatiotemporal precision. Cells perceive cell membrane surface tension via conduits including mechanosensitive ion channels, curvature-sensing proteins (e.g. BAR domain proteins), and cortex-membrane attachment proteins (e.g. ERM proteins). Through membrane receptors like integrins, cells convert mechanical cues into biochemical signals. This conversion triggers cytoskeletal remodeling and extracellular matrix interactions in response to environmental changes. Elevated cell membrane surface tension suppresses cell spreading, migration, and endocytosis while facilitating exocytosis. Moreover, reduced cell membrane surface tension promotes embryonic stem cell differentiation and cancer cell invasion, underscoring cell membrane surface tension as a regulator of cell plasticity. Outstanding questions remain regarding cell membrane surface tension regulatory mechanisms and roles in tissue development/disease in vivo. Emerging tools to manipulate cell membrane surface tension with high spatiotemporal control in combination with omics approaches will facilitate the elucidation of cell membrane surface tension-mediated effects on signaling networks across various cell types/states. This will accelerate the development of cell membrane surface tension-based biomarkers and therapeutics for regenerative medicine and cancer. Overall, this review provides critical insights into cell membrane surface tension as a potent orchestrator of cell function, with broader impacts across mechanobiology.

1. Introduction

The cell surface consists of the cell membrane, underlying actin cortical cytoskeleton, and extracellular matrix. The cell membrane

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is not only an envelope or barrier of assembled actins, but also the primary regulatory factor controlling cytoskeletal dynamics and cell polarity [1]. As a semi-permeable barrier between the inner and outer environments of the cell, the cell membrane defines the physical boundaries of the cell and mediates the interactions between motile cells and their surroundings. In addition, the cell membrane serves as a dynamic platform on which a variety of components - including phospholipids, glycolipids, cholesterol derivatives, as well as transmembrane proteins, and proteins with membrane-binding domains - participate in various aspects of motility. Normally, lipids and membrane proteins are free to diffuse within the membrane unless they are bound to cytoskeletal structures and thus confined. The diversity and dynamics of membranes, determined both by the movement of these molecules and by material transport between the inner membrane and the plasma membrane, reflect the close link between the composition of the cell membrane and its morphology, in which the aggregation of curvature-sensitive lipids and proteins in curved regions further affects the local membrane curvature.

In addition to the biochemical composition, the mechanical properties of the cell membrane, especially cell membrane surface tension, play a decisive role in regulating cell behavior. Although the importance of cell membrane surface tension is recognized, the mechanisms underlying its specific effects on cell behavior have not been fully elucidated. Cell membrane surface tension is defined as the force per unit length acting on the membrane cross-section [2,3] and has rapidly become a fundamental quantitation in the fields of membrane biophysics and cell biology [4]. Cell membrane surface tension arises in part from the in-plane tension required to overcome hydrostatic pressure within the cell, as well as from adhesion forces between the cytoskeleton and the membrane. Cell membrane surface tension imposes a reverse load on anti-membrane extension, which is associated with actin-based protrusion morphologies such as lamellar pseudopods and filamentous pseudopods, as well as a transient separation of the cell membrane from the cytoskeleton driven by transmembrane pressure gradients. In the past, cell membrane surface tension was assumed to be uniform. However, recent research shows that cell membrane surface tension has dynamic, nonuniform attributes [5]. An increasing amount of in vitro experimental data demonstrates that changes in cell membrane surface tension not only affect the overall structure and biomechanical properties of tissues but also influence cell signaling and cell responses. Cell behaviors are altered due to changes in the mechanical and biochemical properties of cell membrane surface tension, exhibiting effects on cell spreading [6], cell migration [7–11], cell invasion [12], cell phagocytosis and cytokinesis [5,13], cell division and differentiation [14–16], etc. Therefore, this article systematically reviews techniques for measuring cell membrane surface tension, explores the propagation and spatial distribution of cell surface tension across the cell membrane, discusses recent findings on how cells sense cell surface tension, and provides a detailed overview of its role in regulating cell behavior.

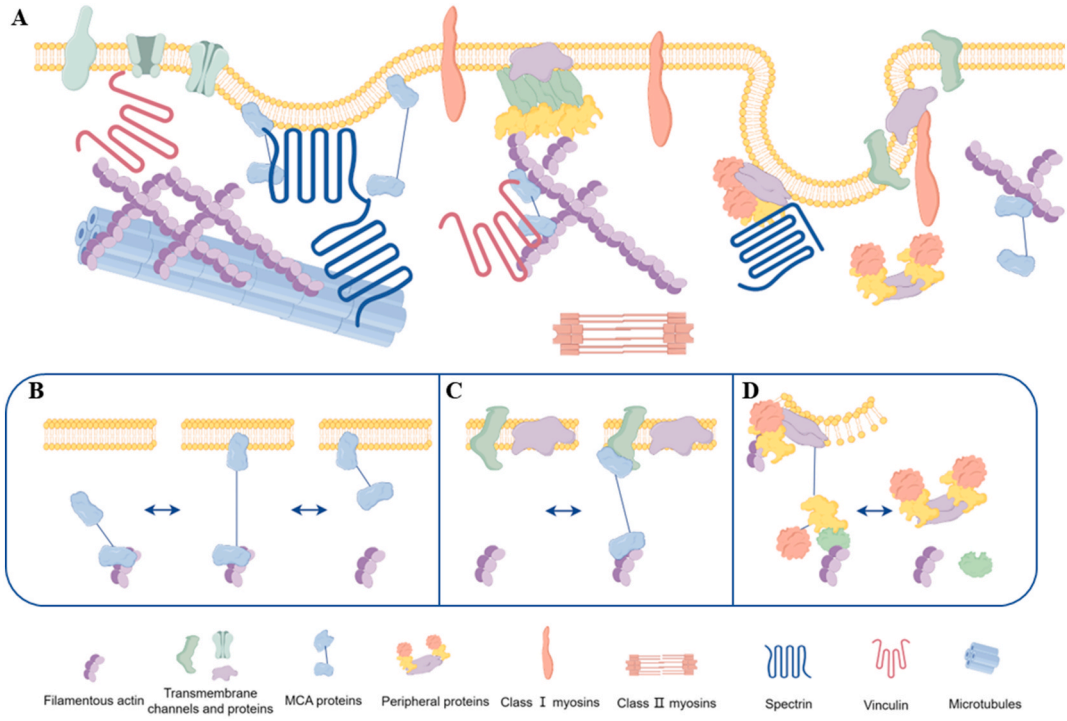

Fig. 1. Schematic representation of cell membranes. (A) The cell surface includes a lipid bilayer and a variety of proteins (associated sugars are not described for simplicity). (B) Examples of membrane-cytoskeleton interactions controlling cell membrane mechanics: Membrane-to-cortex-attachment (MCA) proteins affect cell surface mechanics by dynamically binding to actin and thus influencing surface viscous resistance. (C) Transmembrane proteins can interact directly or indirectly (for example through MCA junctions) with the underlying cytoskeleton and influence the diffusion of other molecules in the plasma membrane. (D) The modular structure of BAR (Bin/Amphiphysin/Rvs) domain proteins allows dynamic remodeling of the plasma membrane and actin cytoskeleton by combining a BAR domain that can sense/generate curvature and accessory domains (SH3, PX, PH, RhoGEF, RhoGAP domains), quoted from Ref. [4].

2. Composition of cell membranes

The cell membrane is a lipid bilayer containing transmembrane and membrane-bound proteins and carbohydrates. These components on the cell surface are closely connected through nonspecific molecular interactions and a unique layer of proteins (such as the ERM (Ezrin, Radixin, Moesin) or Myo1 families), the composition of which differs in various cell types. In addition, the composition of intermediate filaments and spectrin networks protruding from the cell surface to varying degrees also differs depending on the cell type [17] (Fig. 1A). The complexity and dynamic changes in the molecular composition of lipids are essential for membrane structure and function. Lipid types include phospholipids, cholesterol, glycolipids, and sphingolipids, among others [18], which are indispensable for maintaining the integrity and function of the cell membrane. Different cell types and their specific functions require specific membrane lipid composition; for example, the apical membrane of epithelial cells shows greater stability due to its unique lipid composition [17]. Lipid rafts, as special membrane microstructures rich in cholesterol and sphingolipids, play a key role in the regulation of tissue membrane proteins and signaling molecules [19]. The lipid composition of the membrane further affects the curvature, fluidity, and permeability of the membrane, which has an impact on a variety of cellular processes [20]. Lipid metabolism, through the processes involved in synthesis, degradation, transport, and remodeling, constitutes the core mechanism of regulating the lipid composition of cell membranes [21]. Changes in the cell membrane surface tension affected by lipid metabolism can affect lipid accumulation by stretching the lipids and thus affect the lipid composition of the membrane [22]. For example, the phosphorylation regulation of Orm1/2 by Ypk1/2 can effectively regulate lipid synthesis and membrane transport, and alleviate cell membrane surface tension [23]. Studies have also shown that the increase of neutral lipids in the bilayer increases the surface tension of the cell membrane, highlighting the direct link between lipid composition and the surface tension of the cell membrane [24]. In addition, lipid metabolism has an impact on the asymmetric distribution of lipids in the cell membrane, which is related to membrane permeability, potential, stability morphology, and other biological properties [25]. Changes in the cell membrane surface tension also affect the phase behavior and properties of the membrane, such as fluidity and phase transition temperature [26]. These findings are of great significance for further understanding the dynamics and functionality of the cell membrane.

3. Origin of cell membrane surface tension

Cell membrane surface tension refers to the force or stress exerted on the cell membrane, also called effective membrane tension. Mechanically, cell membrane surface tension consists of two major components (Fig. 2): the in-plane tension of the lipid bilayer caused by osmotic pressure, and cortical tension, namely the adhesion force between the cell membrane and cytoskeleton(membrane-to-cortex attachment, MCA) [27,28]. MCA can be characterized by dynamic tether pulling, that is, force measurements are made during pulling on the lipid chain before the lipid flow reaches equilibrium. MCA proteins then act as a moving "barrier" that prevents the flow of lipids toward the tether, creating viscous resistance (Fig. 1B). This viscous drag can be quantified by pulling the rope from the same cell at different extraction speeds and fitting a specific continuum model to a force-velocity curve. In lipid vesicles, cell membrane surface tension can propagate globally due to the two-dimensional liquid nature of the lipid bilayer, which allows its components to diffuse rapidly. In the cell, however, factors such as peripheral protein binding, the presence of transmembrane proteins, and interaction with the basal actomyosin cortex may result in greater and more localized surface tension at the cell membrane than for pure lipid vesicles. These factors provide additional resistance to regional changes and restrict such changes to local regions of the cell.

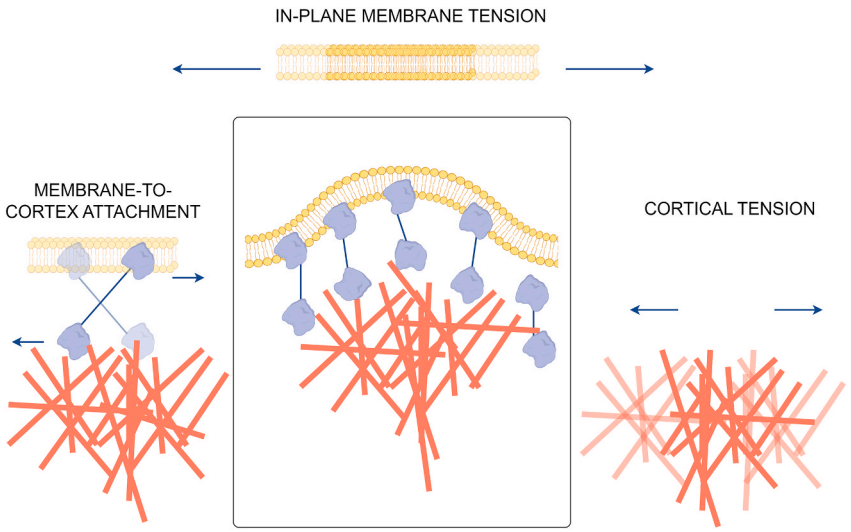

Fig. 2. Schematic representation of cell membrane surface tension components Both the plasma membrane (yellow) and cortex (red) can be described by their tension. In cells, cell membrane surface tension arises from both in-plane tension (the final distance between lipids is exaggerated) and cortical tension, that is, membrane-cortical attachment (MCA, blue).

Studies by Daniels and Turner [29] revealed a numerical range of cell membrane surface tension between (10^{-2}) and (10^{-5}) J/m^2. In sharp contrast, the in-plane tension, or the so-called line tension, experiences a significant decrease of about two orders of magnitude upon the introduction of a particular substance, as documented by Karatekin [30] et al. In addition, cortical tension, another key element of cell mechanics, was found to be approximately (10^{-4}) millethenox/meter (mN/m). The values for in-plane and cortical tension are several orders of magnitude lower compared to the membrane surface tension. The striking differences between these tensions highlight their complex interactions in regulating cellular dynamics. In particular, the integral role of intrapatial and cortical tone in critical processes such as cell migration and division embodies their synergistic effects in maintaining cell integrity and functionality. Further analysis revealed that the ratio of adhesion force to cortical tension is a key factor in determining membrane surface tension, revealing the interdependence between these biophysical parameters. In addition, the regulatory effect of cortical tone is reflected in its ability to translate into excessive hydrostatic pressure within the cell, which is balanced by the osmotic pressure difference across the membrane, and then affects the cell volume and shape. Thus, regulation of excess membrane area is critical for maintaining cellular homeostasis, a process that depends on the combined effects of cortical tension and cell membrane surface tension. This review focuses on cell membrane surface tension that reflects the energy cost to increase membrane area (expressed in J/m^2 = N/m, analogous to the surface tension of a fluid interface).

4. Spatial distribution and propagation of cell membrane surface tension

The published literature contains widely different views on how local changes in membrane surface tension propagate between cells (Table 1). The propagation of surface tension of the cell membrane largely depends on its mechanical properties. If a tension gradient is applied to the cell membrane of a viscous fluid, the fluid flows freely within the film and the cell membrane surface tension propagates globally on a time scale proportional to the viscosity. On the other hand, in cell membranes of semi-solid materials such as gels, there is no long-distance propagation of cell membrane surface tension in the cell over a time scale of ≈10 min. What explains these seemingly opposing views? Experimental studies on cell membranes reveal that their mechanical properties are the key factors determining the non-uniform distribution and local propagation of cell membrane surface tension [5]. This suggests that the response of the cell membrane to the tension gradient is nonlinear and non-Newtonian fluid, a phenomenon that arises from the composition of the membrane and its interaction with the cytoskeleton. Cohen and Shi [31] showed that the blockade of cell membrane surface tension propagation can be explained by transmembrane proteins interacting with the underlying cytoskeleton leading to membrane flow barriers, which may vary in different cell types. Indeed, cortical thickness and architecture vary across cell types and subcellular regions [32,33], as do the expression of MCA and transmembrane proteins. In addition, the binding of these proteins to the basal cytoskeleton also affects the diffusion of other components in the plasma membrane (Fig. 1C) [34]. Another important feature of the cell membrane that contributes to the differences in the propagation of surface tension across the different studies is that it is a 2D structure occupying 3D space. Membrane deformation, also known as membrane curvature, has been extensively studied in vitro in the context of a variety of membrane binding/remodeling proteins [35]. The relationship between membrane tension and membrane curvature in these simplified experimental systems has been well understood [36–38]. Interestingly, MCA proteins such as ezrin can alter their membrane teeling ability by interacting with actin and curvature-sensing binding partners [39]. Thus, differences in cell membrane curvature may affect the propagation of membrane tension by affecting barrier distribution and binding (Fig. 1D).

We summarize a conceptual framework for studying the propagation of cell membrane surface tension within the cell. Many transmembrane proteins are attached to the cytoskeleton and therefore constitute fixed components of the cell membrane. These fixed

Table 1
Summary of the cell membrane surface tension propagating in the cell.

References	Viewpoint	Cell type
Rapid equilibration of cell membrane surface tension		
[40]	As an overall mechanical feedback, membrane tension may constitute a conduit for intracellular information transmission due to its rapid relaxation on a time scale of milliseconds.	Eukaryotic cell
[11]	Lateral membrane tension cannot act locally because of its transient equilibrium at the cell surface.	Fish epithelial corneal stromal cells
[41]	A change in tension in one region can propagate almost instantaneously to the distal region, thus enabling fast cross-region transmission of physical information within the cell.	lymphocytes
[42]	Under assumed static conditions, the membrane tension over the entire membrane appears isotropic and uniformly distributed.	Review
[43]	The protrusion force resulting from actin growth increases the membrane tension nearly fourfold, a phenomenon that is thought to equilibrates rapidly within the cell.	Review
Local changes in cell membrane surface tension		
[44]	Although the fluid nature of the lipid bilayer generally facilitates rapid balancing of forces, it has been demonstrated that local interactions with the cytoskeleton result in nonuniform tension.	T cell
[5]	Within the cell, long-distance propagation of membrane tension does not occur on a time scale of about 10 min.	HeLa, 3T3 fibroblasts, MDCK, mBEC, neurons HeLa, 3T3 fibroblasts, MDCK, mBEC, neurons
[45]	Increased actin polymerization enhanced local membrane/cortical tension	RBL-2H3 cell
[46]	Cell traction forces cause membrane tension to increase in local regions, thereby activating Piezo1 channels in spatial microdomains.	Human foreskin fibroblasts, mouse embryonic fibroblasts, and neural stem/progenitor cells

components are thought to be limiting factors for lipid flow. In other words, the cell membrane bilayer can be viewed as a fluid structure undergoing fluid motion through a porous confinement array. Set $\boldsymbol{\sigma}$ in membrane tension. On the cell membrane produces a tension gradient $\nabla\boldsymbol{\sigma}$, the membrane with $\mathbf{v} = \frac{k}{\eta}\nabla\sigma$ flow speed. Here, η is the viscosity of the lipid bilayer and k is the Darcy permeability representing the ability of the fluid to pass through the porous bulk, a lipid bilayer embedded in immovable obstacles. In 2D dimension, $k \approx -\frac{a^2[1+\ln(\varphi)]}{8\varphi}$ ($\varphi < 0.2$), in which a is the radius of the obstacles, φ for obstacles area fraction [47]. If the cell membrane is subjected to tensile force and meets resistance to flow, then stretching occurs. If the cell membrane is subjected to tensile force and meets resistance to flow, then stretching occurs. After stretching, the cell membrane surface tension will change $\Delta\sigma = E\frac{\Delta A}{A}$, where E represents the stretching modulus and $\frac{\Delta A}{A}$ represents the proportional change in the cell membrane area. Membrane stretching is a highly nonlinear process, that is, the stretching modulus can change depending on the initial state of the membrane or the physiological state of the cell. The tensile modulus can span a wide range (from ≈0 pN μm^{-1} in folded or tubular membranes to ≈ 100 000 pN μm^{-1} in pure lipid bilayers) [3,48]. Once the membrane is stretched, the lipid bilayer gradually flows through the immobile confinement to relieve the stretch. The balance of tensile and viscous forces leads to the diffusion of tension, with a tension diffusion coefficient $D_\sigma = \frac{Ek}{\eta}$. The diffusion coefficient will be corrected by the tensile modulus, and the Darcy permeability and tensile modulus will be included in the modified diffusion coefficient. In this framework, tension does not propagate in membrane reservoirs and folds ($E \approx 0$), but it propagates very fast in follicles with a negligible fraction of immobile confinement area and the cell membrane is stretched. Therefore, the heterogeneous composition and complex structure of the cell membrane results in spatial variations in the diffusion coefficient along the membrane, resulting in a non-uniform and localized tension distribution. Thus, four parameters determine how cell membrane surface tension propagates through the cell: the area fraction φ of the immobile barrier; The size of the obstacle a; The tensile modulus of the cell membrane area E; Membrane viscosity $\boldsymbol{\eta}$. These parameters control the interaction of membrane flow and membrane stretch and together determine the rate at which local changes in surface tension of the cell membrane propagate within the cell.

5. Measurement of cell membrane surface tension

Cell membrane surface tension, as determined by experimental techniques, is a combination of in-plane and cortical tension. The range of membrane surface tension values from different cells is listed in Table 2. Mechanical techniques for measuring cell membrane surface tension include micropipette aspiration [49], and tether-pulling experiments [50]. Chemistry-based methods utilize fluorescent lipid tension reporters [51] (Fluorescent lipid tension reporter, Flipper-TR). In micropipette aspiration, suction is applied upon contact of the micropipette with the cell, drawing a portion of the membrane into the micropipette. According to the Laplace law, the average membrane tension σ can be approximately calculated from the aspiration pressure P and membrane curvature radius r [49], expressed as $\sigma = 0.5Pr$(Fig. 3A). This method has been widely used to study the mechanical properties of lipid vesicles, sea urchin eggs, and red blood cell membranes. However, it should be noted that this technique is only suitable for morphologically simple cells such as lipid vesicles or suspension cells, not complex cells like neurons or neutrophils. Therefore, tether-pulling experiments based on atomic force microscopy and optical tweezers were designed. Lipid chains are pulled out from the cell and the membrane tension σ is calculated from the measured force f to pull the lipid chains and the knowledge of the bilayer bending stiffness κ using $\sigma = f^2/8\pi^2\kappa$ [52] (Fig. 3B). Since the position of the traction force exerted by magnetic beads on the membrane surface determines tension values, a local measurement alone cannot fully capture tension variations along the cell membrane unless multiple tags can simultaneously exert traction and cover a known distance. Another challenge is that the use of magnetic beads to pull the rope may interfere with the cellular processes under study and have an effect by locally altering the internal and external symmetries of the cavity. It may also arise in methods commonly used to manipulate cell membrane surface tension, including pharmacological interventions such as cyclodextrins or changes in cell osmotic pressure. In many cases, the use of recombinant systems, such as giant monolayers of vesicles with controllable lipid composition and protein interactions, has allowed elucidation of how cell-membrane surface tension operates in specific and isolated systems.

Ideally, one would like to measure cell membrane surface tension values in situ within cells. To this end, a novel fluorescent probe Flipper-TR (non-invasive fluorescent probe) was developed. Flipper-TR consists of two large dithiophene (DTT) "flippers" (Fig. 3C–a). In the unconfined environment, the two flippers twist out the conjugate by repulsive forces between the methyl group and the inner ring sulfur, close to the attached rotatable bond. The negatively charged carboxylate in the head group helps to ensure directional insertion into the membrane [56]. Flipper-TR has a high photostability [56] and is almost equally distributed into different membrane phases. Fluorescence absorption/emission spectra differ between lipid phases, which do not change position during phase transitions and do not perturb the membrane order, such as cholesterol [57]. Flipper-TR flattens in response to increased lateral pressure

Table 2
The range of cell membrane surface tensions measured in different systems (this is not an exhaustive list).

References	Methods of measurement	Cell type	Numerical value
[53]	Tether-pulling	Neurons	0.04–0.12 pN/nm
[54]	Tether-pulling	Melanoma cells	11–30 × 10^{-3} pN/nm
[55]	Optical measurement	Red blood cells	0–8 × 10^{-3} pN/nm
[52]	Tether-pulling	Keratinocytes	0.15–0.45 pN/nm
[2]	Theory	Spontaneous tension	2–200 × 10^{-3} pN/nm

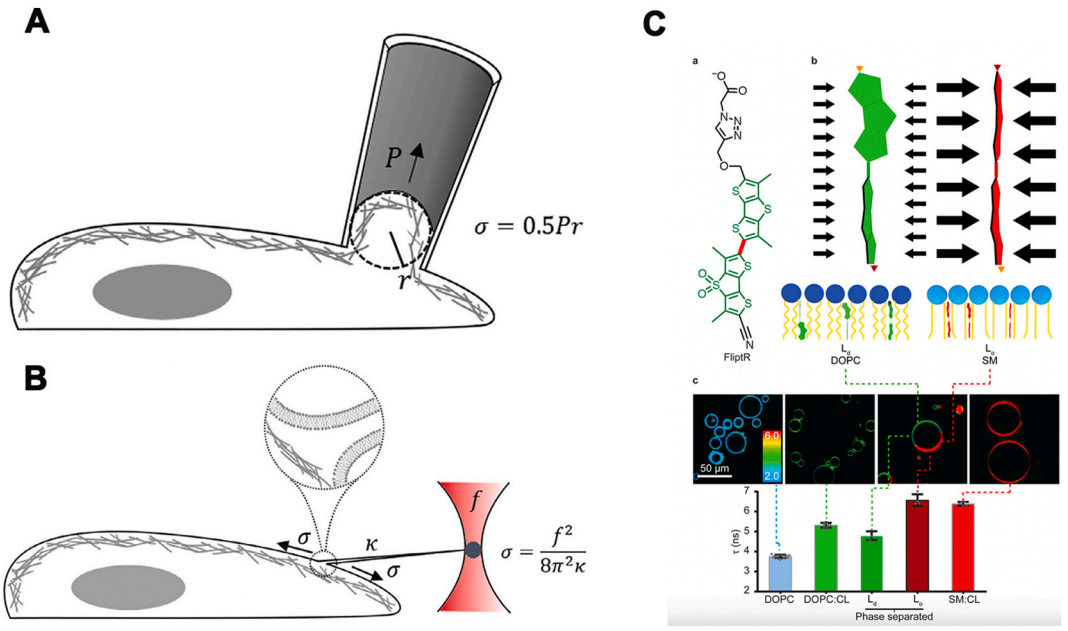

Fig. 3. Schematic representation of the method used to measure the surface tension of the cell membrane (A) Micropipette suction method: a part of the membrane is aspirated into a microtube. According to Laplace's law $\sigma = 0.5Pr$, the average membrane surface tension σ can be approximately calculated from the suction pressure P and the diaphragm membrane radius of curvature r, quoted from Ref. [49]. (B) Tether-pulling experiment: a reactive bead attached to the cell membrane was captured and pulled away by optical tweezers. Flowing lipids enter the tether. By measuring the force f required to pull the tether and the bending stiffness κ of the bilayer membrane, cell membrane surface tension σ of the can be obtained, where $\sigma = f^2/8\pi^2\kappa$, quoted from Ref. [50]. (C) Flipper-TR measures cell membrane surface tension based on fluorescent molecules that are distorted by changes in lipid packing. (a) Chemical structure. Shown in red are the carbon bonds that the fluorophore (green) can wind around. (b) The pressure along the axis of the Flipper-TR probe can planarize the two fluorophores, leading to changes in the excitation maximum and fluorescence lifetime. (c) The fluorescence lifetime τ_1 of Flipper-TR as a function of the lipid composition in the GUV, from the liquid-disordered (L_d) to the liquid-ordered (L_o) membrane. The components were DOPC (N = 5, R = 15), DOPC:CL = 60:40 (N = 5, R = 25), phase-separated DOPC:SM:CL = 25:58:17 (N = 4, R = 5) and SM:CL = 70:30 (N = 5, R = 25). Mean ± SD [51].

(Fig. 3C–b). After calibration, Flipper-TR can be used to measure membrane tensions of MDCK cells, HeLa cells, and Giant Unilamellar Vesicles(GUVs) of specified compositions, and has been applied to yeast, cancer and HeLa-derived cells [58–60]. As an important technical breakthrough, Flipper-TR monitors changes in cell membrane surface tension by altering its fluorescence lifetime as a function of the twisting of its fluorescent moieties [51] and utilizes the linear relationship between fluorescence lifetime and tension for quantitative analysis. This enables facile and accurate measurement of cell membrane surface tensions by fluorescence lifetime imaging microscopy (FLIM), paving the way for acquiring information on cell mechanics. Flipper-TR is fluorescent only after incorporation into the cell membrane and reports the density of lipid packing by changes in the fluorescence lifetime, in the range of 4–6 ns. Lipid stacking is defined as the density of lipid acyl chains: higher lipid stacking indicates tighter and more ordered acyl chains, whereas lower lipid stacking indicates denser and more disordered acyl chains. Thus, the liquid-ordered phase has higher lipid accumulation compared to the liquid-disordered phase. Flattenable Flipper-TR probes can distinguish different phases of different orders [61]. The degree of lipid stacking is higher in the more ordered phase because the pressure exerted by the acyl chains is higher, flattening the Flipper-TR probe. Cell membrane surface tension is also expected to alter lipid accumulation by stretching lipids. However, the area added by stretching is very small, at most 8 % before lysis [48]. The lifetime of Flipper-TR increases with the proportion of lipids forming the liquid-ordered (L_o) phase: the Flipper-TR fluorescence lifetime of GUVs composed only of dioleate glycerophosphatidylcholine (DOPC) (which forms the liquid-disordered phase (L_d) above 0 °C) is 3.75 ± 0.08 ns (mean ± SD, N = 11, R = 43), and the effect of the DOPC and cholesterol(CL) (DOPC: CL 60:40), which increased the lipid order with a fluorescence lifetime of 5.31 ± 0.12 ns (N = 5, R = 15), while the GUV of liquid-ordered phase (L_o) formed by sphingomyelin (SM) and CL (70:30) was 6.39 ± 0.09 ns (N = 5, R = 25). Moreover, when phase-separated GUVs are formed (DOPC: SM: CL 25:58:17), different domains can be easily imaged by measuring Flipper-TR lifetimes (Fig. 3c, L_d and L_o). Interestingly, the lifetime of Flipper-TR in one of the domains is close to that in the DOPC: CL 60:40 film (4.79 ± 0.21 ns (N = 4, R = 5), while the DOPC: CL 60: 40 of 5.31 ns), while the lifetime of the other domain is very close to that of the GUV composed only of SM and CL (6.57 ± 0.29 ns (N = 4, R = 5), whereas SM: CL 70:30 is 6.39 ns). These results indicate that Flipper-TR is sensitive to lipid composition by detecting various stacking of lipids in different phases in different sequences (Fig. 3C–c). This allows fluorescence lifetime imaging microscopy (FLIM) to easily achieve accurate measurement of cell membrane surface tension. Flipper-TR can also be measured in a multicellular environment and has a temporal resolution that is not achievable with conventional rope pull experiments. But the limitation of this method stems from its nature of sensing lipid packing, which depends on cell membrane surface tension and lipid composition. Although cell membrane surface tension can be

uniquely calibrated for different lipid components, changes in membrane composition cannot be detected during measurements.

Recent studies have shown that techniques such as resonant acoustic rheology based on interfacial capillary waves provide a new method to quantify the properties of membrane surface tension [62]. This approach allows non-contact measurements of the viscoelastic properties of biological samples, providing insights into phenomena such as tissue diffusion and cell sorting [63]. In physics, the control and manipulation of surface acoustic waves at the quantum level has been explored for applications in quantum technology [64]. The coupling of surface acoustic waves to superconducting qubits opens up the possibility of precise quantum control in various systems [65]. These advances highlight the interdisciplinary nature of surface tension measurement research and its impact in different fields. The combination of innovative techniques such as resonant acoustic rheology with established methods such as confocal microscopy for high-resolution measurements has great potential to advance our understanding of surface tension in biological and physical systems, thus paving the way for obtaining information about cellular mechanics.

6. Cell membrane surface tension sensing and transduction

Cells can perceive the surface tension of the cell membrane through protein-based mechanosensors or molecular responses mediated by the cytoskeleton and membrane (Fig. 4A). For example, mechanosensitive ion channels. As a highly sensitive mechanical sensor, these channels can rapidly respond to mechanical cues and transduce them into biochemical and biomechanical reactions [66]. Mechanosensitive ion channels function by responding to changes in cell membrane surface tension, with their open probability depending on membrane tension [67], thus serving as one of the important mechanisms for cells to sense cell membrane surface tension. This mechanism has been validated in eukaryotes (MscL ion channels) [68] and primary osteoblasts [69]. Mechanosensitive ion channels can sense changes in cell membrane surface tension over a wide dynamic range, with sensitivity ranging from signals just

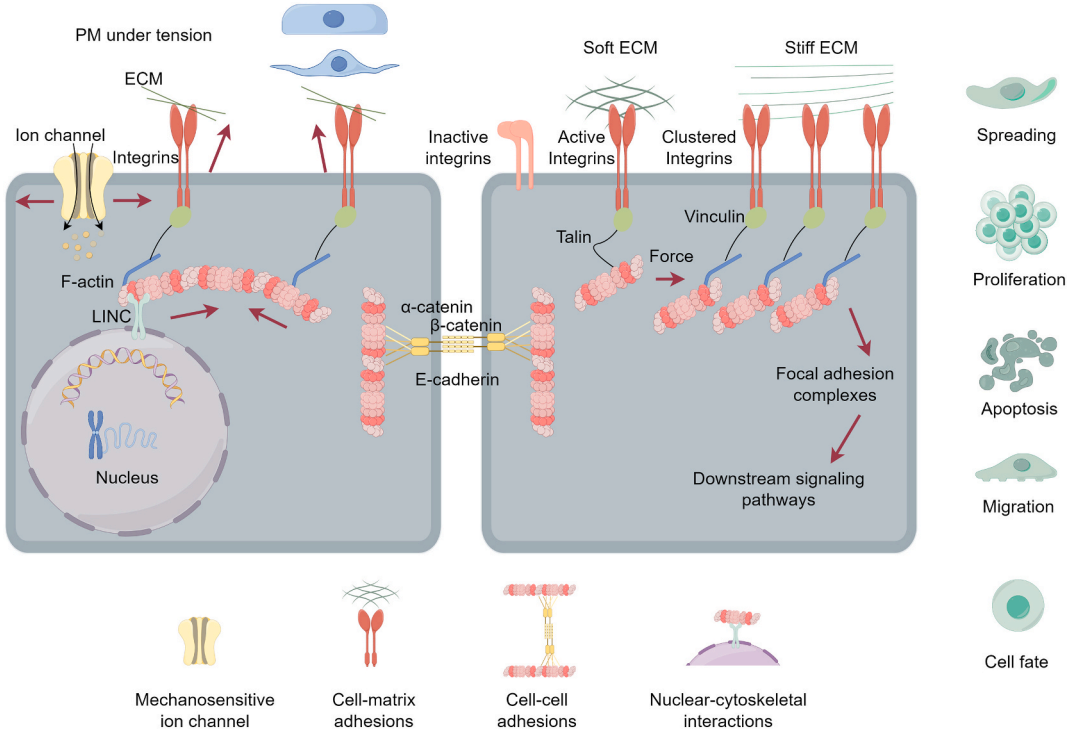

Fig. 4. Molecular mechanisms by which cells sense and respond to mechanical signals and their regulation of cellular behavior (A) Cells have evolved to sense force through protein-based mechanoreceptors or cytoskeleton - and membrane-mediated molecular responses, a process known as mechanosensing. Cells sense membrane surface tension in a variety of ways, including mechanosensitive ion channels, integrins, cadherins, and nuclear membrane proteins in cytoskeletal interactions (B). Cells then convert these mechanical signals into biochemical signals and elicit biological responses through mechanotransduction processes. Initial activation and binding of focally adherent integrins to the extracellular matrix (ECM) can occur in the presence of low resistance (soft ECM), resulting in the formation of transient focal complexes in which the connection between integrin intracellular domains and actin is weak. In the presence of high resistance (hard ECM), adaptor proteins are recruited to promote integrin aggregation, actin remodeling, and myosin-mediated contraction, thereby increasing cell membrane surface tension. Stress proteins (such as talin) undergo conformational changes induced by external forces, which promote the local recruitment of other proteins (such as vinculin) and strengthen their connections with actin to regulate local signaling and provide a positive feedback effect to further enhance and perfect local adhesion. Subsequently, multiple mechanisms help to regulate downstream signaling pathways and mediate biological behaviors generated in response to mechanical signals. (C) The biological responses of different cell types to surface tension-derived mechanical signals are diverse. Cell membrane surface tension can affect cell spreading and cell division, regulate cell endocytosis and exocytosis, guide cell migration and cell invasion, etc.

above thermal noise in hair cells [70] to set points near the lytic tension of MscL ion channels [68]. In addition, significantly increasing or decreasing cell membrane surface tension can be achieved by perturbing the transmembrane ion gradient and influx/efflux of water. Methods utilizing osmotic changes to manipulate cell membrane surface tension have been widely applied in research [9,10,71,72], however, whether cells employ such mechanisms to actively regulate their membrane tension remains to be further studied in depth. Although bidirectional channels that increase cell membrane surface tension are known to gate bacterial mechanosensitive ion channels [73–75], increasing the open probability of MscL ion channels, these channels are nonspecific, also controlling an unrelated bacterial mechanosensitive ion channel MscS ("S" stands for smaller conductance). Other cell membrane surface tension sensing candidate channels such as Piezo1 and Piezo2 open in response to various mechanical stimuli including stretching [76,77]. This channel has been implicated in the differentiation of multiple types of stem cells. In adult Drosophila, Piezo channels sense mechanical stress and regulate midgut endocrine stem cell differentiation through Ca^{2+} signaling [78]. A similar mechanism applies to the neuronal and glial lineages of human neural stem/progenitor cells, where traction forces activate Piezo1, leading to Ca^{2+} influx and nuclear translocation of YAP [79].

In other cases, key mechanosensing structures such as integrins [80] and cadherins [81] are surface receptors that enable cell-ECM interactions and cell-cell interactions. Both of these interactions are linked to the actin skeleton, thereby enabling mechanical signaling between the exterior and interior. Starting outside the cell, the first elements to encounter biophysical cues are extracellular matrix (ECM) molecules. For example, the fibronectin (FN) III domain containing an integrin binding site can withstand forces of up to 80–200 pN [82]. This is a form of mechanical transduction, as mechanical stress exposes hidden binding sites in these domains, thereby promoting integrin adhesion and further driving fibronectin fibril formation [83]. Second, mechanoreceptors on the cell surface adjust the structure in response to external stress or changes in ECM stiffness. Specifically, to enhance ligand binding capacity, integrins undergo a conformational change from a folded state to a stretched state to accommodate the rigid ECM (Fig. 4B). Tension may be generated by coupling of the cadherin complex to the actomyosin membrane cortex when adhesive contact between cells first occurs. Prolonged cadherin adhesion elicits active cellular mechanisms that enhance tension, including activation of myosin II (such as RhoA) signaling and enhancement of actin assembly (nucleated by Arp2/3 and formin) signaling that connects the actin cytoskeleton.

Membrane-to-cortex attachment (MCA) proteins are proteins that provide connections between the cell membrane and the actin cytoskeleton. MCA proteins can not only play structural support roles, but also sense cell membrane surface tension by mediating attachment of the actin cortex to the membrane [15,84]. Recent research shows that the activity of some MCA proteins is regulated by external forces. Candidate proteins include ezrin [85] and single-headed myosins and membrane-associated myosins of the myosin 1 family. Both can simultaneously interact with the cytoskeleton and cell membrane. Ezrin A is an actin-binding protein that mediates localization of the actin cytoskeleton and interacts with FilGAP (Rac specific GTPase activating protein). High cell membrane surface tension leads to increased loss of this interaction, triggering Rac activation and actin polymerization [86]. Myosin 1c (Myo1c) is a protein with actin-related motility that can dynamically provide cell membrane surface tension to enhance mechanosensitive ion channel sensitivity [87]. Additionally, myosin 1b (Myo1b) significantly alters its motility properties under external force. Studies have found that under 2 pN forces or less, the dissociation rate of myosin 1b from actin decreases 75-fold. This indicates that myosin 1b can interact more firmly with the cytoskeleton when the cell experiences external forces [88]. MCA proteins are involved in limiting the expansion of membrane area and regulating in-plane tension of the lipid bilayer, thereby influencing overall membrane tension [15, 89]. The tension generated by MCA proteins represents the combined effects of in-plane tension in the lipid bilayer, membrane bending rigidity, and membrane-to-cortex adhesion forces [50]. In summary, MCA proteins are indispensable in mechanotransduction, mediating attachment of actin cortex to the membrane and thus playing a vital part in sensing and responding to cell membrane surface tension.

The last force-sensitive element is the plasma membrane itself, whose membrane curvature can be affected by local membrane tension. Finger-like protrusions (membrane bending) that point to the cell-cell interface are observed when cells form so-called "focal adherens junctions". They are commonly found in migrating endothelial cells [90–92] and reflect differences in contractile forces across junctions. Many membrane curvature-related proteins possess sensing, stabilizing and generating domains for curvature [93], such as Bin/amphiphysin/Rvs-(BAR-) domains (including BAR and I-BAR proteins) or Amphipathic Lipid Packing Sensor-(ALPS-) domains [94]. BAR domains sense and generate membrane curvature by interacting with membrane phospholipids [95]. Studies demonstrate that high cell membrane surface tensions can reduce I-BAR protein binding by limiting membrane curvature required for their binding [96]. In this way, many GEFs (Guanine nucleotide Exchange Factors) and GAPs (GTPase-activating proteins) with membrane curvature sensing domains can regulate GTPase activity in a tension-dependent manner [97]. Meanwhile, ArfGAP1 containing an ALPS domain tends to bind to positively curved membranes (as produced during vesicle formation) or areas of lipid packing defects. ArfGAP1 preferentially induces GTPase hydrolysis of Arfs in these areas [98,99]. Additionally, single proteins (such as amphiphysin I) can also sense and produce high membrane curvature at the leading edge of cells. Amphiphysin I is an effector protein containing a BAR domain involved in regulating endocytosis in cells. Its ability to sense or induce curvature depends on its density on the membrane [100]. The relationship between membrane curvature and the accompanying free energy of membrane adhesion provides valuable information for understanding proteins' ability to sense membrane curvature [101]. Studies have found that upon binding, curvature-sensing proteins may alter local membrane morphology through one or more curvature-driving mechanisms [102]. Studies have further validated that cell membrane surface tension can counteract the deformation of membranes caused by curvature-generating proteins [103]. Additionally, protein-induced membrane curvatures change local membrane tension, with lipids flowing accordingly during protein adsorption to accommodate the curvature change [104]. Membrane curvature sensing proteins play a key role in monitoring and responding to changes in membrane morphology and membrane surface tension.

Subsequently, the cell converts these physical signals into biochemical signals through a series of adaptor proteins and second messengers. In the compliant matrix (soft ECM), integrins may occur upon initial activation and binding to the extracellular matrix

(ECM) and form transient foci in which the intracellular domains of integrins are loosely attached to the actin cytoskeleton. As matrix stiffness (hard ECM) increases, integrins aggregate and initiate the recruitment of local focal adhesion signaling molecules, which triggers a signaling cascade and causes cells to remodel their cytoskeleton to regulate internal tension between each other. Many proteins involved in integrin adhesion undergo mechanosensitive unfolding to promote further growth and reinforcement of focal adhesion. For example, applying a force of 12 pN can unfold the talin protein, reveal the hidden binding site, and trigger the vinculin protein to bind to it [105]. Once bound to talin protein, it will promote the recruitment of intracellular plaque proteins by the cytoplasmic tail of b-integrin and promote the assembly of focal adhesion [106]. In addition, multiple mechanisms contribute to the regulation of downstream signaling pathways that mediate biological responses to mechanical signals.

Cells then translate these mechanical signals into transient responses or sustained cellular behaviors (Fig. 4C). Cells can generate a sustained response to mechanical stress by altering their gene expression. For example, high tensile stress can activate fibroblasts into ECM-producing and modified myofibroblasts, thereby remodeling and hardening the surrounding ECM [107]. Upregulation of ECM-related proteins can generate a positive feedback mechanism whereby cells change the composition, organization, and elasticity of their surroundings in response to mechanical forces. This mechanical interaction mechanism gives cells the ability to adjust their behavior.

7. Cell membrane surface tension regulates cell behavior

Cells in vivo reside in different mechanical environments, for example, cells in blood circulation undergo motion and deformation under fluid flow while cells in other tissues experience varying extents of stretch and compression. As a result, cell membrane surface tension exhibits nonuniform distribution and is subject to continual changes. Changes in cell membrane surface tension, whether caused by external forces (such as blood flow) or internal mechanisms (molecular motors, actin flows, and altered connections between cell membrane and cytoskeleton), can regulate the unique and complex physical system on the cell surface, enabling cells to rapidly respond to surrounding forces and elicit corresponding biological effects. Examples include cell spreading, cell migration, cell invasion, cell division, and differentiation, as well as cell phagocytosis and exocytosis.

7.1. Mechanical regulation of cell spreading

Cell spreading refers to the process of cells adhering to the matrix and extending the cell membrane to cover larger areas, forming a flattened morphology. This process is crucial for various cell functions including adhesion, migration, and proliferation [108]. Cell spreading typically involves the following steps: (1) early formation of adhesion sites between the cell and substrate; (2) protrusions of peripheral pseudopodia of the cell; (3) new adhesion site formation between pseudopod tips and the substrate; (4) cessation of cell spreading when driving forces and resisting forces reach equilibrium (Fig. 5). At the initial stage of cell spreading when the cell first contacts and forms initial adhesion sites with the substrate, intracellular stress fibers have yet to form and changes in the cytoskeleton can be ignored [109], similar to the wetting behavior of a viscous droplet on a surface [110]. Thus, cell membrane surface tension

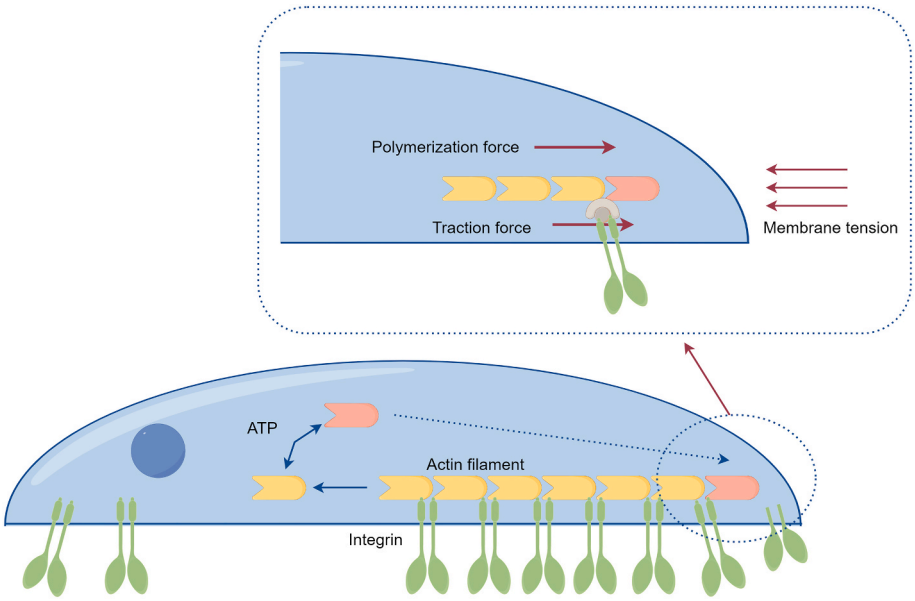

Fig. 5. Schematic diagram of the cell spreading process. At the leading edge of the cell spreading direction, the convergent force generated by the polymerization of actin filaments, and the binding of integrins to the extracellular matrix generate a tensile force on actin filaments to drive the spreading process, while the cell membrane surface tension acts as a hindrance.

remains largely unchanged during the early spreading process [111]. To form lamellae pseudopodia during cell spreading, growing actin filaments must generate sufficient local force to displace the cell membrane [7,9,112]. Indeed, actin-based protrusions can increase the surface tension of the cell membrane because the membrane is creased by the converging forces during cell spreading. Assuming a constant cell volume (determined by cell osmotic pressure), changes in cell surface area lead to corresponding alterations in membrane tension. Experiments have validated [112,113] that cell membrane surface tension impedes pseudopod protrusions. Increased cell membrane surface tension results in decreased cell spreading rates; On the contrary, chemical methods that reduce membrane tension lead to an observable acceleration in lamellipodial extension speeds in cells [114], triggering a global activation leading edge signal [10]. Given that the leading edge can potentially contribute to tension, any variation in its size prompts immediate compensatory adjustments to align with the prevailing level of membrane surface tension, thereby establishing a homeostatic mechanism.

Additionally, the regulation of cell membrane surface tension involves the adhesion between the membrane and cytoskeleton, as well as changes in cytoskeletal tension, which subsequently impact cell spreading and adhesive assembly [115]. For example, EphB, a regulator of E-cadherin endocytosis and adhesion, was shown to promote cell spreading during zebrafish morphogenesis [116–118]. Focal adhesions are the most extensively studied type of adhesion complex formed by adherent cells and are enriched with integrins. This complex comprises over 100 different proteins that participate in signal transduction and force transmission [119]. Integrins, transmembrane proteins capable of forming αβ heterodimers, recognize specific extracellular matrix ligands. In humans, there exist 18α isoforms and 8β isoforms that bind similar ligands in various combinations [120]. The intracellular domain of integrins facilitates actomyosin-based force transmission to the extracellular environment through interactions with adaptor proteins such as talin, α-actinin, and vinculin bound to actin microfilaments [121–123]. As crucial membrane receptors on the cell surface, integrins exert mechanical tension essential for cell adhesion and migration processes by binding to surface ligands [124]. This mechanical force exerted by integrins plays a central role in activating signaling pathways driving cell movement. Moreover, cell surface tension significantly influences cell spreading speed by regulating both the mechanical properties of the cell surface itself and its adhesion to the matrix. The dynamic interplay between membrane surface tension and actin dynamics is vital for coordinating cellular spreading processes. Furthermore, it is important not to overlook how gradient variations in cell membrane surface tension regulate cell movement or how a rigid matrix environment affects pseudopodia formation and cytoskeleton-membrane junction proteins involved in migration towards a rigid matrix [125].

7.2. Mechanical regulation of cell migration

Another important cell behavior regulated by cell membrane surface tension is cell migration. Cell migration is essentially a dynamic process of morphological protrusions and retractions, which is vital for normal embryogenesis, neurogenesis, immune function, and angiogenesis. Additionally, cell migration is also associated with pathological processes such as cancer cell invasion and metastasis [126]. During cell migration, the actin machinery acts as a power source to lengthen membrane protrusions by pushing and/or pulling the membrane, forming new adhesion sites at the leading edge, and detaching the cell membrane at the rear. These processes are not only regulated by cell membrane surface tension but also influence its changes. Moreover, obstacles and geometric cues may also locally perturb cell membrane surface tension. Thus, cell membrane surface tension serves as a key mediator of mechanosignal transduction, playing an important role in regulating cell migration [1,10]. For example, actin polymerization leads to increased cell membrane surface tension at lamellipodia, which may impede the formation of other lamellipodia at distal sites to enhance the cell's ability to persistently migrate in a specific direction. In this context, Hetmanski et al. [59] have discovered that fast-migrating cells establish a positive feedback control of cell retraction by sensing membrane tension. Cryptic lamellipodia activate the RhoA-ROCK1/PKN2 pathway to regulate local F-actin organization and contraction, promoting retraction at the cell rear. The resulting feedback loop between cytoskeletal signals and membrane tension leads rapidly migrating cells to constrict rapidly to complete migration cycles, providing directional memory in complex matrices to drive persistent cell migration. These findings align with the role of EHD2 in migrating cells [127]. Petrie and Yamada [128] have found that cells may migrate in different modalities in matrices of varied mechanical properties. For example, nonlinear elastic materials trigger lamellipodial spreading of cells, while elastic materials promote pseudopodial extension and migration. This phenomenon may be due to myosin II retaining actin filaments at a low tension state through binding, and coupling to ECM through cell-ECM adhesions. Sensing changes in cell membrane surface tension, cells respond by increasing myosin contractility to modulate cell migration [129]. On the other hand, some experiments have observed an inhibitory effect of membrane tension on pseudopod protrusions [112]. For instance, Batchelder et al. [130] have found that high membrane tension decreases pseudopod protrusion distances but increases overall cell migration velocity. Additionally, membrane tension can modulate leading cell velocity and tension distribution in collective cell migration, highlighting its impacts on collective cell behaviors [131]. Membrane tension also regulates cell motility by controlling the direction and speed of triple-negative breast cancer cell migration, emphasizing its role in cancer cell migration [125].

7.3. Mechanical regulation of cell differentiation

Existing studies have shown that cell membrane surface tension can regulate the differentiation of embryonic stem cells (ESCs). Cohen and Chen [132] discussed the mechanical control of stem cell differentiation, emphasizing the significance of mechanical factors including cell membrane surface tension in regulating stem cell differentiation. Bergert et al. [15] utilized static tether pulling experiments based on atomic force microscopy to measure cell membrane surface tension during early differentiation of ESCs, finding that ESCs detach the membrane from the underlying actin cortex, reducing membrane confinement by cortical actin when

transitioning to a differentiated state, thereby lowering cell membrane surface tension. Differentiating cells exhibited decreased membrane surface tensions from (41.3 ± 5.25) pN to (30 ± 5.92) pN compared to undifferentiated ESCs, revealing cell membrane surface tension can regulate the differentiation capability of ESCs. In contrast, mechanically confining the membrane to the cortex by enhancing Ezrin protein activity or expressing synthetic signaling-inert crosslinkers to increase membrane tension in ESCs resulted in ESCs maintaining their initial multipotent characteristics without differentiating. The research by Belly et al. [133] has revealed that decreased cell membrane surface tension may inhibit early differentiation of embryonic stem cells, further confirming the key role of cell membrane surface tension in regulating stem cell conversion into specific cell types. Similarly, Belly et al. [16] have found that during early differentiation stages, ESCs alter morphology through RhoA activity reduction and subsequent decreases in membrane tension mediated by β-catenin. Since phosphorylation of ERM proteins exhibited significant expression changes during early differentiation, and β-catenin mediated such phosphorylation, comparative experiments were conducted to measure and compare levels of phosphorylated ERM proteins and membrane tension magnitudes in embryonic stem cells with and without β-catenin knockout. Statistical data showed 75 % lower phosphorylated ERM protein expression and about 30 % reduction in cell surface tension with β-catenin knockout. The decreased ERM phosphorylation mediated by β-catenin led to correspondingly lower ESCs membrane tensions compared to before differentiation. Hence high cell membrane surface tensions would impair early ESCs differentiation. These results reveal close links between morphological and mechanical attributes, and demonstrate embryonic stem cell early ontogeny is regulated by intrinsic and extrinsic physical factors. Additionally, cell membrane surface tension plays a role in mechanical signals in development and tissue repair. In vascular regeneration at zebrafish wound sites, the downstream portion of the damaged vessel extends preferentially. Upstream of the injury, luminal pressure generated by blood flow causes a stretch of endothelial cells, and the increased membrane tension inhibits membrane protrusions via suppressing the TOCAeN-WASPeArp2/3 pathway. In contrast, no elevated luminal pressure is present downstream, enabling leading edge formation and promoting wound closure [134].

7.4. Mechanical regulation of cell division

In addition to regulating ESCs differentiation, cell membrane surface tension also has the function of regulating cell division. Taneja et al. [14] used micropipette aspiration to measure cell membrane surface tension and found that the actomyosin II (MII) filament component can regulate the tension of the cell cortex surface, thereby characterizing the roles of MIIA and MIIB proteins in cell division. The results showed that MIIA can increase cell membrane surface tension to promote cell division speed, while MIIB plays a role in maintaining morphological stability, preventing chromosome misaggregation leading to morphological instability, and mediating late cytokinetic abscission. This study revealed that the MII-regulated mechanism of cell membrane surface tension is crucial for maintaining normal cell division. In addition, cell membrane surface tension has a regulatory role in the orientation of cell division, a view supported by the study of Campinho et al. [135] on spindle orientation, cell elongation, and tissue tension alignment in the enveloping cell layer (EVL). cell membrane surface tension can induce intercellular mechanical coupling to achieve rapid communication at the cellular scale [52]. Moreover, cell membrane surface tension not only regulates subcellular processes but also coordinates cell behavior at longer length scales [51,84]. Chugh et al. [33] found that actin network architecture and myosin activity are key factors regulating cell surface tension. Tension gradients generated by cellular activity (such as cell division) regulate these processes [136,137]. Léon [138] showed the importance of cell membrane surface tension in physiological processes such as cell division, migration, or spreading. Mochizuki et al. [139] found that cell division and E-cadherin mediated adhesion regulate epithelial cell movement by modulating epithelial tension. Additionally, caveolae that regulate cell membrane surface tension are known to localize to the abscission site of dividing cells [140]. When force is applied to the plasma membrane and actin cortex, cell membrane surface tension propagates rapidly within the cell [141]. Gradients in cell membrane surface tension can induce cell shape changes, thereby promoting processes like cell division and migration [142]. In mitotic cells, the increased membrane tension requires the actomyosin cytoskeleton to assist in overcoming the increased load incurred during clathrin-mediated endocytosis [143]. Cortical contraction generates surface tension, thereby creating geometries feasible for division in physically-constrained environments [144]. Serres et al. [145] showed that cortical waveform protein has a controlling effect on the organization and mechanics of the actin network during mitosis, which is crucial for the successful division of enclosed cells. cell membrane surface tension, membrane trafficking, and osmotic pressures influence the mechanical characteristics of cell division [146].

7.5. Coupled cell endocytosis and exocytosis

Cell endocytosis is a complex process through which cells carry out substance exchange and physiological metabolism. In the endocytosis process, extracellular substances are enveloped by the plasma membrane, the plasma membrane invaginates inward and further forms vesicle membranes, and finally, the vesicle membrane separates from the plasma membrane and enters the cell interior, producing a series of physiological activities and functions. Low membrane tension promotes endocytic vesicle transport by enhancing vesicle formation [147], manifested as an increase in membrane tension that counters the aggregation of coat proteins. When endocytic vesicles form, the plasma membrane actively bends inward, while membrane tension resists the inward bending of the plasma membrane, thus membrane tension is inversely related to the rate of endocytosis [13,148–150]. In vitro experimental results show that the force produced by the aggregation of clathrin to the membrane is on the same order of magnitude as the range of membrane surface tension, typically 10^{-4} N/m, and endocytosis can be effectively inhibited by increasing membrane tension to prevent clathrin aggregation and assembly on the plasma membrane [151]. Recent research shows that increased membrane tension can inhibit endocytosis in secretory cells. In secretory cells, overcoming the energy barrier imposed by lateral tension is a limiting factor for the rate of endocytosis [152]. Abella et al. [153] reported a Sla2-based FRET tension sensor that can be used to measure the

force exerted by the actin network on the plasma membrane during endocytosis in yeast. Using this sensor, they measured endocytic forces in the range of 300–880 pN, and showed that this force requirement is lowered when membrane tension decreases. Riggi et al. [60] showed that in addition to regulating phosphorylation of endocytic proteins independently, TORC2 also controls endocytosis by regulating membrane tension. The increased membrane tension after TORC2 inhibition affects endocytosis in two ways: (1) it severs linkages between PM-tethering proteins Sla2 and Ent1 and the actin cytoskeleton; (2) it impedes recruitment of Rvs167, an N-BAR containing protein important for vesicle scission at endocytic sites. With an acute increase in membrane tension, an adaptation of endocytosis, exocytosis, and lysosomes can be observed, further revealing the dynamic response characteristics of endocytosis to changes in membrane tension [154]. On the other hand, reduced cell membrane surface tension has been shown to activate the dynamic-independent CLIC/GEEC endocytosis pathway in a neotin-dependent manner [155]. Focal adhesion proteins are components of focal adhesion that are sensitive to mechanical forces. By applying local forces to focal adhesion, integrin clusters, another transmembrane component of focal adhesion, disintegrate and are internalized through clathrin-mediated endocytosis [156]. Focal adhesion thus represents a hub of communication between cell-surface mechanics and intracellular processes, including transport. These results emphasize the importance of biophysical cues in regulating cellular and molecular processes.

Changes in membrane tension not only affect endocytosis but also exocytosis [157]. High membrane surface tension can promote exocytosis by lowering the energy barrier for vesicle fusion and exposing hydrophobic lipid tails. On the other hand, membrane tension can counteract SNARE-mediated membrane fusion [157]. During cell expansion, membrane reservoirs first unfold until reservoir depletion causes a sudden increase in membrane tension. This triggers exocytosis of vesicles to supply endogenous membrane to the plasma membrane [9,158]. This mechanism also functions in phagocytosis, where immune cells ingest large particles like pathogens or apoptotic cells, enhancing exocytosis of vesicles containing GPI-anchored proteins to provide the membrane area needed for efficient internalization [159]. Additionally, membrane tension appears to determine the mode of exocytosis. In fibroblasts, exocytosis usually occurs through complete collapse fusion, while in neurons and neuroendocrine cells with lower plasma membrane surface tension, “kiss-and-run” exocytosis (a form of exocytosis where the vesicle releases its contents through a transient pore) is prevalent [42,160,161]. In neuroendocrine chromaffin cells, sufficient vesicle fusion requires ATP-driven actin assembly to generate enough plasma membrane surface tension [162]. In summary, membrane tension and endo/exocytosis regulate each other through different feedback mechanisms in various systems.

7.6. Mechanical regulation of cell invasion

The most dangerous aspect of cancer is its metastatic progression. Cancer cells are exposed to potentially destructive blood flow dynamics, including fluid shear stress (FSS) [163], during the process of metastasizing to distant sites. Circulating tumor cells (CTCs) need to survive under FSS, have higher energy demands, and maximize energy metabolism efficiency through Rho-actomyosin and formin-mediated pathways [164,165]. In addition, to prevent membrane rupture induced by FSS, membrane reservoir safety must be ensured by coupling plasma membrane and actin cytoskeleton remodeling to adapt cells to changes in mechanical stress [166]. Although these studies have focused mainly on the cell deformability capacity of CTCs, cell membrane surface tension is a direct parameter controlling the driving force required for metastatic migration. Physical deformability and stiffness determine whether cancer cells can “squeeze through” a confined space during invasive metastasis, while cell membrane surface tension determines whether cancer cells can “move forward.” Therefore, these two physical parameters may interact to promote the invasion-metastasis cascade.

Recent advances have been made in understanding the relationship between cell membrane surface tension and tumor malignancy. KRasV12 mutation in MCF10A cells causes abundant signal fluctuations in the basement membrane [167]. Dephosphorylation of PIP2, a major regulator of cell membrane surface tension, can reproduce this phenomenon, suggesting that cell membrane surface tension forms a threshold for the Ras-ERK pathway. This is consistent with a recent finding that PIP2 is essential for maintaining cell epitheliality [168]. Importantly, cancer cell invasiveness is inversely correlated with cell membrane surface tension. Decreased cell membrane surface tension enables BAR/F-BAR proteins to provide actin polymerization driving force that deforms the cell membrane and promotes vesicle- or actin/ruffle-based cancer cell motility [169]. BAR proteins have been reported to be required for invasive cell motility in various cancer cells [170–174]. Although the adaptive molecular mechanisms of cell membrane surface tension during metastasis remain unclear, interestingly, cell membrane surface tension may be linked to cancer stemness. Decreased cell membrane surface tension has been reported to increase tumor stemness [175]. Transplantation of malignant breast cancer cells into mice showed that increased cell membrane surface tension by sustained active form of ezrin not only inhibits cancer cell metastasis but also significantly inhibits cell proliferation [169]. However, the relationship between tumor stemness and cell membrane surface tension warrants further investigation.

8. Conclusion and prospect

Cell membrane surface tension is a key physical parameter regulating various cell behaviors and functions. As reviewed above, important progress has been made in recent years in methods for measuring membrane tension, such as micropipette aspiration, string pulling experiments, and fluorescence lipid tension reporters like Flipper-TR. These tools can quantify membrane tension more precisely and elucidate its roles in cells. The mechanisms by which cells sense cell membrane surface tension are also being revealed. Mechanosensitive ion channels, curvature sensing proteins, and membrane cortical cytoskeleton attachment proteins can all transduce changes in membrane tension into biochemical signals. Further study of the interactions between these mechanoreceptors will provide a clearer picture of how cells integrate mechanical signals from cell membrane surface tension.

Many key cellular processes are influenced by cell membrane surface tension. During cell spreading and migration, cell membrane surface tension provides a counterforce to actin protrusions, thereby guiding cell motility. Decreased cell membrane surface tension promotes cancer cell invasion, partially by enhancing membrane deformability. In contrast, increased cell membrane surface tension inhibits proliferation and stemness. cell membrane surface tension also initiates endocytosis and exocytosis through biophysical and signaling mechanisms. In addition, tension gradients across cells can drive polarization, diffusion, division, and tissue morphogenesis. Although cell membrane surface tension has significant effects at the single cell level, an interesting research prospect is to explore how its effects propagate across larger distances to coordinate multicellular behaviors and tissue mechanics, providing new ideas for disease diagnosis and treatment, tissue engineering, regenerative medicine, etc. Current measurements of cell membrane surface tension are mainly through in vitro cell experiments, but the real survival environment of in vivo cells is much more complex, which will inevitably affect the measurement of its parameters. On the one hand, in vivo cells may be subject to direct mechanical loading from adjacent cells, extracellular matrix, and other organs; on the other hand, the biological behaviors of cells in vivo may also affect cell membrane surface tension. Many in vitro experimental results are difficult to reproduce in in-vivo experiments, and the difference between in vitro and in vivo environments is an important factor. How to establish the correlation between cell membrane surface tension parameters from in vitro experiments and the in vivo environment remains to be explored.

Secondly, the basis for establishing correlations between cell membrane surface tension and biological behaviors is mainly the overall phenomenology of cells, i.e. inferred from the final state of cell observation. The dynamic evolution laws of submicroscopic-level and molecular-level structures and functions of cells and organelles remain unclear. The quantitative and threshold relationships between cell membrane surface tension and biological behaviors also need to be explored. In addition, from the clinical application point of view, the correlation between cell membrane surface tension, biological detection index, and biological behavior needs to be clarified. Specifically, in terms of how to regulate cell membrane surface tension, we need to quantify the diffusion and binding dynamics of MCA proteins and understand how they are affected by membrane topological structures. To this end, we need new tools with high spatiotemporal control capabilities that are validated in a large number of biological systems, because cell membrane surface tension can play diverse roles depending on cell function or state. In addition, applying these tools to study the roles of other cytoskeletal components (such as microtubules or intermediate filaments) in membrane mechanics would be meaningful.

Clearly, changes in cell membrane surface tension play a crucial role in regulating cell fate and guiding tissue-specific development. It not only affects the overall structure and biomechanical properties of the organism, but also affects the signals transmitted to the cell, thereby regulating cell responses. With the increasing discoveries of how cell membrane surface tension regulates cell spreading, drives cell endocytosis and exocytosis, enhances cell migration, and guides cell differentiation, an ongoing and future challenge in cancer prevention and treatment has been and will continue to be how to finely tune the physical parameters of cell membrane surface tension and understand how its components individually or jointly regulate cell behaviors in order to effectively simulate the occurrence and development of tumor cells. This will undoubtedly also become a research hotspot in the field.

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No data was used for the research described in the article.

CRediT authorship contribution statement

Manqing Li: Writing – original draft. **Xiumei Xing:** Writing – review & editing, Supervision. **Jianhui Yuan:** Writing – review & editing, Supervision. **Zhuoying Zeng:** Writing – review & editing, Visualization, Funding acquisition.

Declaration of competing interest

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Please let me know if you need any modifications to this declaration or have additional details to include. I'm happy to assist further as needed.

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