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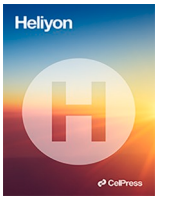

Review article

Aging-related changes in the mechanical properties of single cells

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ABSTRACT

Mechanical properties, along with biochemical and molecular properties, play crucial roles in governing cellular function and homeostasis. Cellular mechanics are influenced by various factors, including physiological and pathological states, making them potential biomarkers for diseases and aging. While several methods such as AFM, particle-tracking microrheology, optical tweezers/stretching, magnetic tweezers/twisting cytometry, microfluidics, and micropipette aspiration have been widely utilized to measure the mechanical properties of single cells, our understanding of how aging affects these properties remains limited. To fill this knowledge gap, we provide a brief overview of the commonly used methods to measure single-cell mechanical properties. We then delve into the effects of aging on the mechanical properties of different cell types. Finally, we discuss the importance of studying cellular viscous and viscoelastic properties as well as aging induced by different stressors to gain a deeper understanding of the aging process and aging-related diseases.

1. Introduction

The mechanical properties of cells are pivotal for various cellular functions, including gene expression, migration, and maintaining homeostasis [1,2]. Furthermore, these mechanical properties can be influenced by changes in metabolic processes in response to external forces and aging, through cytoskeleton rearrangement or distortion of the cell and its intracellular components [3,4]. In general, the mechanical properties encompass both elastic properties such as stiffness, elastic modulus (Young's modulus), strength, and elasticity, as well as viscous properties such as viscosity and relaxation time, collectively also referred to as viscoelastic properties. It should be noted that some studies distinguish between mechanical properties and viscoelastic properties. Mechanical properties primarily describe the elastic response of a solid material to applied forces, whereas viscoelastic properties describe how a material responds to forces over time, exhibiting both elastic and viscous behavior. However, in this review, we use these terms interchangeably.

Various methods have been developed to accurately quantify the mechanical properties of single cells. These methods include atomic force microscopy (AFM) [5], particle-tracking microrheology [6], optical tweezers/stretching [7], magnetic tweezers/twisting cytometry [8], microfluidics [9] and micropipette aspiration [10] (Fig. 1). AFM has long been a widely used indentation method for quantifying high-resolution mechanical properties at the subcellular or cellular level [11,12]. The system consists of a cantilever with a

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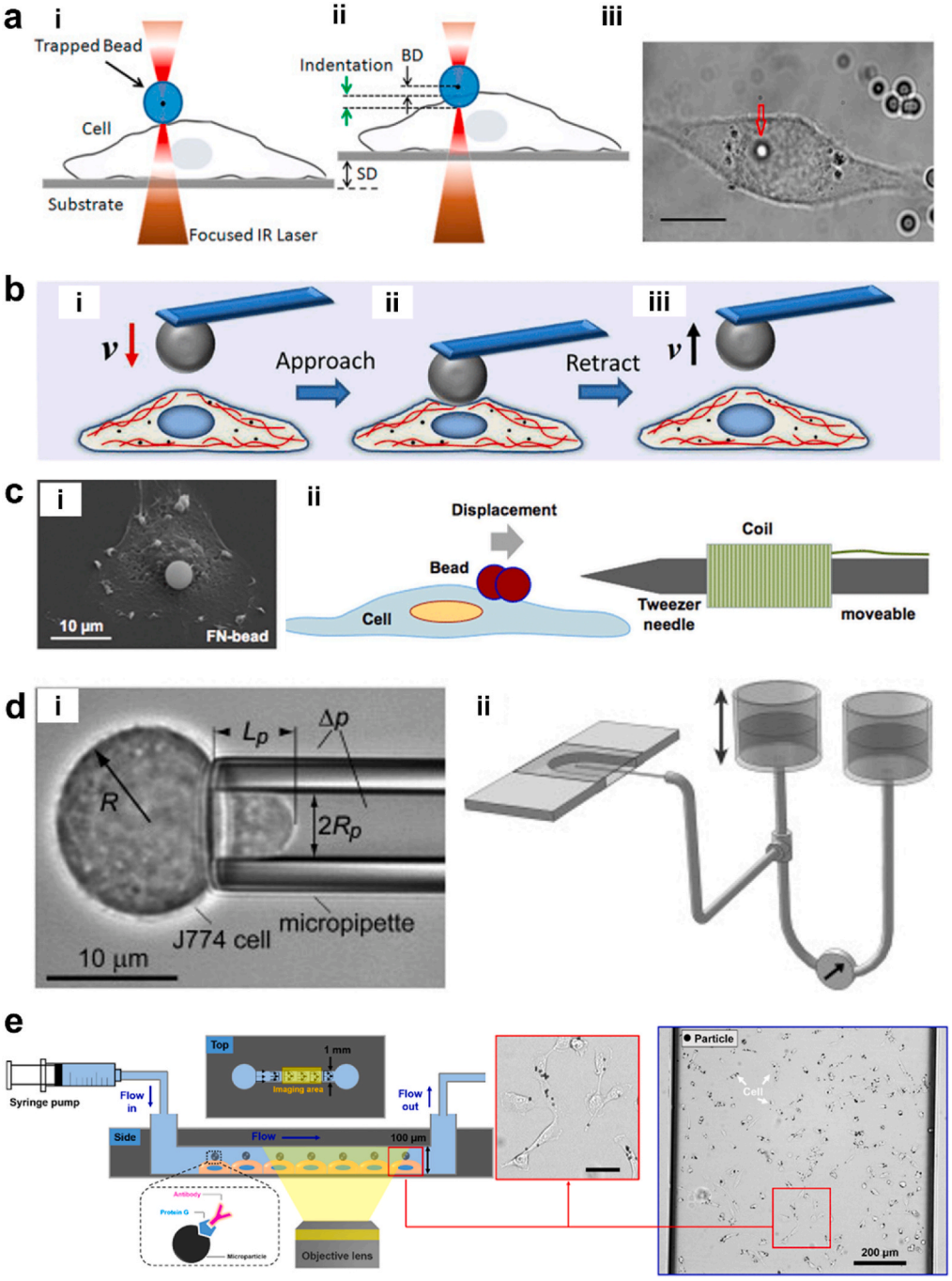

Fig. 1. Schematics of mechanics-based systems to measure cellular mechanical properties. **a**. Optical tweezers: (i) The cell is situated beneath the trapped bead and (ii) the stage is elevated, causing the cell to interact with the bead, while the bead indents the cell. (iii) An optical microscope image displaying the bead positioned above the cell, as indicated by the red arrow. Scale bar: 10 μm. Figure adapted with permission from Ref. [7], copyright Optics and Lasers in Engineering. **b**. Atomic force microscopy (AFM): (i) The AFM probe first descends against the cell surface at a constant loading speed, denoted as *v*. (ii) The indentation force is measured throughout the deformation process. (iii) The probe subsequently retracts away from the cell surface at the same speed (*v*). Figure adapted with permission from Ref. [5], copyright Physical Review Research. **c**. Magnetic tweezers: (i) A representative scanning electron microscopy (SEM) image depicting a fibroblast with a fibronectin-coated bead. (ii) The magnetic force is generated by a magnetic field gradient using a magnetic tweezer needle, causing the superparamagnetic bead to move. Figure adapted with permission from Ref. [8], copyright Scientific Reports. **d**. Micropipette aspiration method: (i) A macrophage (J774) is aspirated using a micropipette. (ii) The micropipette is connected *via* tubing to a pressure control and measurement system. Figure adapted with permission from Ref. [10], copyright Biophysical Journal. **e**. Microfluidics: Cells are introduced into a microfluidic channel and subsequently exposed to particles coated with anti-integrin antibodies, specifically designed to bind to integrin molecules on the cell surface. Hydrodynamic forces are

induced through the utilization of a syringe pump and tubing system. The inset, demarcated by a red box and scaled at 50 μm, displays cells bound by the particles. A comprehensive view of the entire field captured in an image for high throughput analysis is depicted within the blue box. Within this image, black dots signify particles adhered to cells, as indicated by white arrows. Figure adapted with permission from Ref. [9], copyright Scientific Reports. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

known stiffness that acts like a spring and can detect any deflection. The tip of the cantilever is pushed onto an adherent cell at a predetermined force, and the resulting resistance force from cell deformation is measured through its deflection. This deflection is recorded via laser deflection focused on the cantilever, captured using a photodetector, providing mechanical properties such as cell stiffness by fitting the curve of force versus indentation. Particle-tracking microrheology is another technique frequently used for analyzing the distribution and movement of fluorescently labeled micron-sized beads embedded in the cytoplasm of live cells [6,13]. The trajectories of the beads and mean square displacement data can be utilized to understand the viscous and elastic properties of the cytoplasm. Furthermore, optical tweezers/stretching involves the stretching of a single cell trapped between optically active beads. This method allows for the cell to undergo varying degrees of stretching by displacing one bead while keeping the other stationary. The stretching is performed at a constant strain rate and various velocities to obtain stretching cycles, which result in a force-extension curve that determines the cell stiffness.

Magnetic tweezers/twisting cytometry is a unique technique that involves attaching micron-sized magnetic beads to cells and subjecting them to force or stress [14–16]. These beads are typically coated with fibronectin or collagen to help them attach to adhesion receptors such as integrins. The beads adhere to the integrins on the cell surface and anchor tightly to the cytoskeleton *via* focal contacts. After attachment, these beads are subjected to an oscillatory or stationary magnetic field, causing them to rotate and impart mechanical torque on the cell. The mechanical properties of the cell, including stiffness and adhesion/bond strength, can be obtained from this movement and displacement of the beads. Moreover, microfluidics is used to study cell deformation and mechanical or viscoelastic properties upon the application of physical or chemical stimuli with ultra-high throughput [9,17]. There are three main microfluidics-based methods to study cellular mechanical properties, namely i) micro-constriction, ii) extensional flow, and iii) shear flow. These techniques are a powerful method for studying the mechanical properties of a large number of cells with high spatial and temporal resolution in a short time. Additionally, micropipette aspiration uses suction pressure to measure the mechanical or viscoelastic properties of a single cell [18,19]. This technique involves connecting a glass capillary (micropipette) to a pressure-based controller at negative pressure and bringing it closer to a cell under a microscope. The cell is initially sucked onto the micropipette tip and then drawn inside the tube. During this process, the cell membrane is aspirated and progressively deformed. This movement can be monitored using a microscope, and the deformation value is further used to quantify mechanical properties such as Young's modulus.

Techniques such as magnetic twisting cytometry and particle-tracking microrheology have been more frequently used to investigate changes at the cytoplasmic level of cells [20]. Meanwhile, AFM, optical tweezers, magnetic tweezers, and micropipette aspiration study cell stiffness by examining changes in both cytoplasmic and membrane components [11,21]. Each method offers distinct spatiotemporal resolutions, facilitating complementary mechanical assessments of cells or tissues [22].

The measured mechanical properties of cells depend on a cell's pathological or physiological state, measurement method, and applied theoretical model, thereby showing a wide range of values of the estimated mechanical properties [23]. As such, cellular mechanical properties are closely linked to the onset and progression of various diseases, making them effective biosensors or indicators for assessing disease states [24]. Research has shown that most cancer cells exhibit greater deformability and lower stiffness compared to normal healthy cells. This characteristic is due to the necessity of their ability to penetrate minute areas, such as blood vessel walls, during migration and metastasis. The aged chondrocytes in osteoarthritis, an age-related degenerative disease, exhibited reduced stiffness compared to normal young cells [25]. Malaria-infected red blood cells tended to lose their deformability and become more rigid [26,27].

Cellular mechanical properties undergo substantial changes with age, albeit varying depending on the cell type. Previous studies have assessed key mechanical properties, including stiffness, elastic modulus, viscosity, and relaxation time, to elucidate the impact of aging on cellular mechanical properties. However, the measurement of mechanical properties in aging cells has predominantly focused on a limited number of cell lines or types, such as vascular smooth muscle cells, fibroblasts, or others. Therefore, expanding the range of cell types analyzed could provide deeper insights into diverse physiological phenomena in different tissues or organs, or age-related diseases. In this review, we will first provide a concise overview of aging-related changes in mechanical properties exhibited by various cell types, along with a brief description of biochemical and morphological changes. Next, we will explore current limitations and propose avenues for future research in this field.

2. Mechanical properties and behaviors of aging/aged cells

For years, scientists have been measuring the mechanical properties of aging/aged cells using various different methods, yet the range of cell types or lines used for these measurements remains limited, considering the approximately 200 types of cells found in the mammalian body. Commonly studied cell types include vascular smooth muscle cells (VSMCs), erythrocytes, leukocytes, fibroblasts, endothelial cells (ECs), cardiomyocytes, and more (Table 1).

Erythrocytes (red blood cells) play a pivotal role in oxygen delivery [28]. To date, numerous studies have examined the impact of aging on cellular mechanical properties. There is a consensus that cellular mechanical properties, such as stiffness or elastic modulus, tend to increase with age, suggesting a decrease in membrane deformability [29]. Furthermore, viscous properties such as viscosity

Table 1
Impact of aging on cellular mechanical properties.

Cell Type	Measurement method	Key Feature	References
Rat Vascular Smooth Muscle Cells	Magnetic twisting cytometry (MTC)	- VSM cells isolated from the thoracic aorta of young (8 months) and aged (30 months) rats - ~0.6 Pa/nm for aged and ~0.18 Pa/nm for young on the matrix rigidity of 1 kPa	[47]
Rat VSMCs	Atomic force microscopy (AFM)	- VSM cells isolated from young (4 months) and old (24 months) male rats - ~ 10 kPa in stiffness for young and ~18 kPa for old VSM cells	[49]
Monkey VSMCs	AFM	- VSM cells isolated from the thoracic aorta of young (5–8 years) and old (24–25 years) monkeys −3.5 kPa for young and 21.6 kPa for aged cells (612 % increase in elastic modulus)	[62]
Monkey VSMCs	AFM	- VSM cells isolated from the thoracic aorta of young (6.4 ± 0.1 years) and old (25 ± 0.4 years) male monkeys - ~10 kPa in modulus of elasticity for young and ~42 kPa for aged cells	[48]
Primary Human Pulmonary Artery SMCs	AFM	- Cells collected from lung tissues of old (50–60 years) and young (11–25 years) donors - No age-related changes in the cellular stiffness ranging from 10 kPa to 15 kPa	[50]
Human Foreskin Epithelial Cell	AFM	- *In vitro* aged cells (>50 population doublings) and young cells (<25 population doublings) - Nuclear region: 14 kPa (young) and 33 kPa (aged) - Cytoplasmic area: 37 kPa (young) and 110 kPa (aged) - Edge of the cell: 0.57 kPa (young) and 2.2 kPa (aged)	[58,59]
Rat Cardiac Myocyte	AFM	- Cells isolated from young (4 mo) and old (30 mo) male Fischer 344 x Brown Norway F1 hybrid rats - AFM: 35.1 ± 0.7 (young) and 42.5 ± 1.0 kPa (old)	[53]
Human Dermal Fibroblast	Optical stretcher	- Cells isolated from 14 human donors aged 27 to 80 years old - Fibroblasts from older donors showed an approximately 60 % increase in rigidity compared to cells from the youngest donors. - Plateau Young's modulus: ~150 Pa (young) and ~250 Pa (old)	[37]
Primary Human Dermal Fibroblasts	AFM	- Cells isolated from 30-, 40-, and 60-years old volunteers - The magnitude of elastic moduli varies depending on the indentation depth (200 nm vs 600 nm). - Age 30: 8 kPa–13 kPa - Age 40: 9 kPa–14 kPa - Age 60: 9 kPa–17 kPa	[41]
Human Dermal Fibroblasts	AFM	- Cells isolated from disposal tissue of circumcision (male, 13 and 14 years old) - The passage number ranging from 5 to 20 was utilized to induce different aging. −0.356 N/m in average stiffness at passages 5 and 1.186 N/m at passages 15	[63]
Primary Human Foreskin Fibroblast	AFM	- Cells from older donors (>30 years) and young donors (<25 years). - Fibroblasts from the young donor group exhibit, on average, greater stiffness compared to fibroblasts from the aged donor group.	[42]
Primary Human Articular Chondrocytes	Micropipette aspiration	- Cells isolated from donors with ages 18–35 and 55+ - Viscoelastic properties were measured - Instantaneous modulus: ~0.4 kPa for ages 18–35 and ~1 kPa for 55+ - Apparent viscosity: ~1.9 kPa s for ages 18–35 and ~2.4 kPa s for 55+ - Relaxation time: no difference between ages 18 –35 and 55+ with ~22 s	[55]
Bovine knee Chondrocytes	AFM	- Cells isolated from neonatal (1 day), adult (5 year) and geriatric (12 year) bovine knees - At indentations exceeding 500 nm, adult chondrocytes (~0.75 kPa) exhibited a significantly lower elastic modulus compared to neonatal cells (~1 kPa). - The intrinsic viscosity of geriatric chondrocytes (~0.27 kPa s) was found to be lower compared to neonatal cells (~0.43 kPa s).	[56]
Human Articular Chondrocytes	AFM	- Cells prepared from surgical specimens of patients with OA, aged 21 to 81 years - Stiffness: ~0.0348 N/m for old cells (patient age: older than 65 years) and ~0.0960 N/m for normal cells (21–45 years)	[25]
Human Single Fiber	Quick release experiment and the slack-test procedure	- Biopsy specimens percutaneously isolated from the vastus lateralis muscle under local anesthesia in two groups: young men (N = 6, aged 25–36 years) and old men (N = 6, aged 60–74 years). - The instantaneous stiffness per force unit was significantly greater in type I and IIa fibers in old men than young men.	[60]
Human Erythrocytes	Micropipette aspiration	- Cells collected from human males aged 21–35 years, and newborn infants aged from 38 to 40 weeks. - Both elastic modulus and viscosity were higher for adult cells than infant cells - Extensional elastic modulus (10^{-3} dyn/cm): ~5 for neonatal RBC and ~6.1 for adult RBC - Plastic viscosity coefficient (10^{-2} dyn/cm): ~0.96 for neonatal and ~2 for adult	[31]
Human Erythrocytes	AFM	- Cells isolated from blood samples obtained by venipuncture of healthy donors - Oxidative stress-induced cellular aging using peroxynitrite	[64]

(*continued on next page*)

Table 1 (*continued*)

Cell Type	Measurement method	Key Feature	References
		-Elastic modulus: ~19 MPa for control and ~22 MPa for peroxynitrite-treated cell	
Human Endothelial Cells	AFM	- HUVEC line was treated with oxidized low-density lipoproteins (ox-LDL, 10 μg/mL) to emulate the cellular aging - Young's modulus: 0.36 ± 0.02 kPa for control cells and 0.76 ± 0.14 kPa for ox-LDL cells	[44]
Human Tendon Stem/Progenitor Cells (TSPC)	AFM	- TSPCs isolated from elderly patients (63 ± 14 years) and young patients (28 ± 5 years). - Elastic modulus: 13.8 kPa (young) and 19.5 kPa (elderly)	[61]
Mouse $CD4^+$ and $CD8^+$ T Cells	Micropipette aspiration	- Cells collected from peritoneal leukocytes of 'adult' (40 ± 4 weeks), 'mature' (56 ± 4 weeks), 'old' (72 ± 4 weeks) and 'very old' (90 ± 4 weeks) - Both $CD4^+$ (0.5 kPa–2 kPa) and $CD8^+$ cells (1 kPa–4 kPa) tend to increase their stiffness with age.	[39]

also exhibited an increase or remained unchanged as individuals age, mirroring the trend observed in elastic modulus [30]. One of the early findings showed that neonatal erythrocytes' elastic modulus was 18 % smaller compared to adult cells, while membrane surface viscosity exhibited similar characteristics in both cell types [31].

The changes in elastic and viscous properties are highly linked to structural, biochemical or molecular changes during aging Erythrocytes, composed of cytoskeletal elements, actin, and spectrin, undergo significant structural alterations with age. Research indicates a marked increase in the complexity of these cytoskeletal components during aging (Fig. 2a). Furthermore, there is a documented upregulation in the expression of lipids or proteins such as hemoglobin. The morphological characteristics of erythrocytes, including surface area and volume, undergo modifications throughout the aging process [32]. The previous study revealed that aging-related ATP depletion results in an increase in the average size of the 2D lattice mesh, consequently affecting cell elasticity [33]. Moreover, as the concentration of calcium ions increases during aging, it can trigger rearrangements in the membrane skeleton structure, ultimately leading to the augmentation of erythrocyte stiffness [34]. The interaction of reactive oxygen and nitrogen species with erythrocytes induces alterations in the membrane, resulting in changes in cell elastic moduli [35]. More specifically, the exposure of erythrocytes to these reagents in high concentrations resulted in elevated erythrocyte elastic modulus.

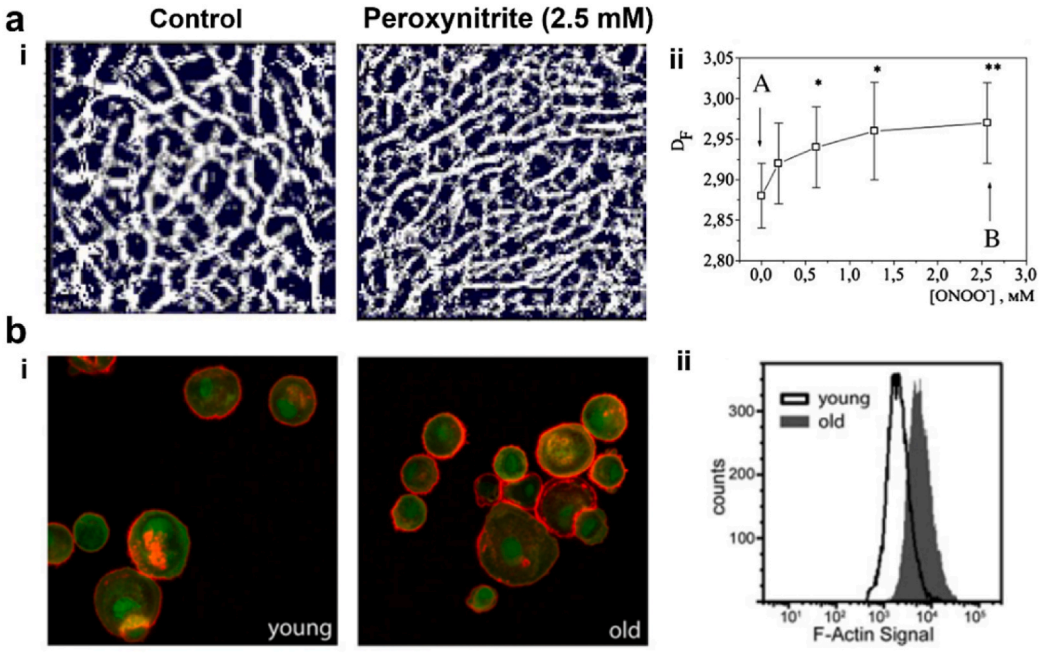

Fig. 2. Aging-related structural changes of the cells. **a**. The effect of aging on the membrane structure of erythrocytes. (i) Membrane skeleton structure of erythrocytes without and with peroxynitrite (an oxidizing agent). (ii) The effect of peroxynitrite (ONOO-) concentration on the complexity of the membrane structure. The increasing peroxynitrite concentration correlates with higher membrane complexity. Figure adapted with permission from Refs. [29,36], copyright Ageing Research Reviews and Bioelectrochemistry. **b**. The impact of aging on F-actin and actin polymerization. (i) Fluorescence images depict the G-actin monomer (green) and F-actin cortex (red) in suspended fibroblasts isolated from young and old donors. (ii) Enhanced F-actin signals observed in cells from older donors. Figure adapted with permission from Ref. [37], copyright Biophysical Journal. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Leukocytes (white blood cells) are integral components of the immune system, actively engaged in both the innate and humoral immune responses [38]. Circulating within the bloodstream, they initiate inflammatory and cellular responses in reaction to injury or pathogens. Leukocytes are mostly short-lived, typically having a lifespan of only a few months or less. Compared to erythrocytes, leukocytes are known to be larger but less deformable. Studies have demonstrated that aging T lymphocytes' stiffness is greater than young T lymphocytes. More specifically, both $CD4^+$ cells (0.5 kPa–2 kPa) and $CD8^+$ cells (1 kPa–4 kPa) tend to increase their stiffness with age [39]. The increase in stiffness or elastic modulus during aging might be attributable to the increased basal F-actin as well as cytoskeletal rearrangements. Furthermore, the mechanical response of aged leukocytes was found to be delayed [29].

Fibroblasts are specialized biological cells responsible for synthesizing the extracellular matrix and collagen, thereby creating the structural framework (stroma) essential for animal tissues [40]. Different types of fibroblasts, including those derived from the human foreskin or the dermis, have been employed to explore the impact of aging on alterations in mechanical characteristics. Experimental findings have been inconsistent across studies. In most cases, studies have concluded that cellular stiffness increases with age [37,41], likely due to the increased F-actin content and actin polymerization (Fig. 2b). In contrast, a conflicting study has shown that fibroblasts from young donors exhibit greater stiffness compared to those from older donor cohorts [42].

ECs form a monolayer lining every blood vessel, regulating exchanges between the bloodstream and the adjacent tissues [43]. The prior study displayed that when human umbilical vein ECs (HUVECs) were treated with the aging-causing factor, oxidized low-density lipoproteins, their stiffness significantly increased compared to those without treatment [44]. Furthermore, shear stress driven by fluid flow is found to serve as a prominent stressor that triggers cellular aging or senescence. Studies have demonstrated that shear stress can elevate the elastic modulus of bovine aortic endothelial cells exposed to shear stress for a day compared to cells without such stress [45]. This increase in elastic modulus may be attributed to the formation of stress fibers at both the cell's ventral surface and middle plane.

VSMCs are the primary components of the blood vessel wall and play a crucial role in regulating blood pressure [46]. The

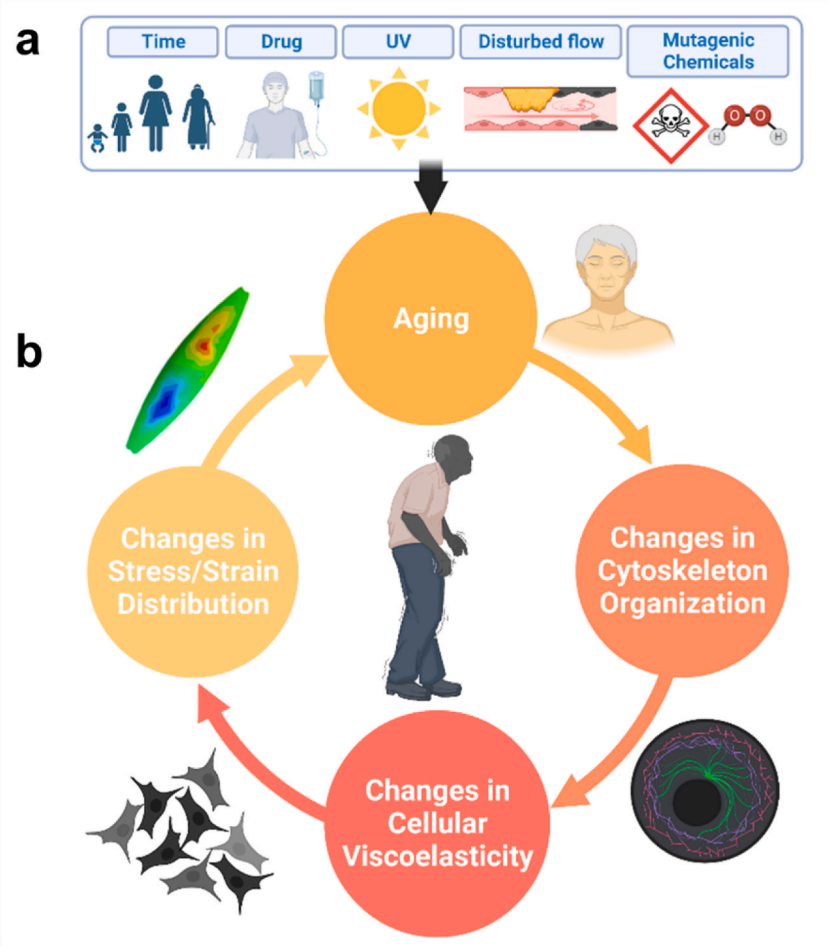

Fig. 3. Aging-induced changes in molecular, structural, and mechanical changes and their connection. **a**. Aging can be induced by various stressors, including drugs, UV light, chemicals, disturbed flow, and other factors. **b**. Aging triggers changes in cytoskeletal density or organization, leading to alterations in cellular mechanical or viscoelastic properties. Consequently, these changes drive modifications in cellular kinetics (stress) and kinematics (strain).

mechanical properties of VSMCs have been extensively studied across various species, including humans, monkeys, and rats. While many studies have indicated an increase in stiffness or elastic modulus with advanced age [47–49], one study found no difference in mechanical properties associated with aging, displaying cellular stiffness ranging from 10 kPa to 15 kPa [50].

Cardiomyocytes (cardiac muscle cells) are contractile and excitable cells in the heart that are striated, branched, rich in mitochondria, and under involuntary control [51]. Studies have shown that the stiffness of cardiomyocytes tends to increase with increasing age. The experimental investigation performed by Lieber et al. using AFM revealed that the apparent elastic modulus of myocytes from old rats (30 months) was approximately 20 % higher than that of myocytes from young rats (4 months), possibly due to alterations in cytoskeletal proteins [52,53].

Chondrocytes and osteocytes play a key role in the formation of cartilage and bone, which protect the body's internal organs, provide structural support, and serve as attachment surfaces for muscles [54]. Prior investigations have demonstrated that osteocytes and chondrocytes possess an elastic modulus of 1–2 kPa and 0.5 kPa, respectively [29]. The early study using AFM exhibited that aged chondrocytes are less stiff than normal young cells [25]. However, a contradictory study utilizing the micropipette aspiration technique demonstrated a significant increase in the elastic modulus with osteoarthritis due to cytoskeletal reorganization [54]. Of note, certain studies have assessed both viscous properties, such as viscosity and relaxation time, along with elastic properties. Steklov et al. showed that apparent viscosity values are ~1.9 kPa s for age 18–35 and ~2.4 kPa s for 55+, while no difference in relaxation time (~22 s) is found [55]. However, in another study investigated by Chahine et al. [56], the intrinsic viscosity of geriatric chondrocytes (~0.27 kPa s) was found to be lower compared to neonatal cells (~0.43 kPa s).

Epithelial cells are highly prevalent in covering the skin, body cavities, and blood vessels [57]. The AFM study conducted by Berdyyeva et al. unveiled that human foreskin epithelial cells exhibit increased stiffness with age in three different regions of the cells: nuclear, cytoplasmic, and edge regions of the cells [58]. This augmented stiffness in aging cells is likely attributable to the heightened density of F-actin microfilaments. However, the application of the actin polymerization inhibitor, cytochalasin B, was found to reverse the stiffness of aging cells [59].

In addition to the aforementioned cells, other cell types, such as skeletal muscle fibers [60] and tendon stem/progenitor cells [61], have demonstrated an elevation in mechanical properties such as stiffness or elastic modulus with aging.

3. Discussion

The fundamental components of cells, such as the plasma membrane, cytoskeleton, and organelles, collectively influence the mechanical behaviors of cells. In particular, cytoskeletal components, such as actin filaments, intermediate filaments, and microtubules, and their associated proteins such as myosin are crucial to maintain the architecture and mechanical properties of cells. As such, it is essential to understand how their structure, content, density, and organization vary with age.

Numerous studies have demonstrated a significant change in cellular mechanical properties with age across various cell types. Collectively, several common explanations have been proposed for this phenomenon. First, the density or organization of cytoskeletal components, such as F-actin (filamentous actin), is strongly correlated with changes in cellular mechanical or viscoelastic properties due to their dynamic alterations with age. These changes result in the modification of cellular kinetics (stress) and kinematics (strain) (Fig. 3b). The early study revealed a notable increase in the content of F-actin in dermal fibroblasts from older donors (aged 61–71) compared to those from younger donors (aged 20–27) while maintaining the level of expression of G-actin (globular actin) [37]. Another study illustrated that the stiffness of human lymphocytes increases during aging, attributed to the elevated F-actin content coupled with a lower reduction in stimulus-induced actin polymerization [65]. Furthermore, increased expression levels of cytoskeletal crosslinkers, such as fascin or α-actinin, along with heightened stress fibers and cytoskeleton density, are implicated in altering cellular mechanical properties. Research has identified that aging epithelial cells exhibit heightened stiffness attributable to the elevated density of cytoskeletal crosslinkers and increased stress fiber density [22]. Another potential explanation is that cholesterol and lipid peroxidation levels increase in aging cells, leading to a consequent rise in cellular stiffness [66].

Biological cells exhibit a dual nature, displaying both solid and fluid characteristics [67]. This viscoelastic behavior, highly influenced by components such as the cytoskeleton, cytosol, and cell membrane, remains crucial in understanding cellular function and dynamics [68]. For instance, the expression of cytoskeleton proteins such as actin, vimentin, and tubulin affect the cellular elastic properties [69]. To support this hypothesis, changes in the viscoelastic properties of chondrocytes and their role in osteoarthritis were studied [69]. The fluidity and viscosity of the cell membrane and cytoplasm define the rheological or viscous properties of the cell, playing an essential role in maintaining intracellular transport [70,71]. Furthermore, intracellular organelles are involved in mechanosensing and are generally connected to the cell cytoskeleton; the external application of mechanical stress to the cell and its organelles can lead to the activation of mechanosignaling pathways [72]. Studies have established that cell metabolism and mechanics are interlinked [3]. Collectively, various organelles significantly contribute to the mechanical properties of the cell.

Currently, the majority of studies have focused on characterizing or quantifying elastic properties such as stiffness or elastic modulus. In contrast, only a limited number of studies have examined viscous or viscoelastic properties despite cells being composed of both solid and fluid components. The viscous properties of cells are closely linked to various cellular functions, molecular diffusion, signal transduction and gene expression. Consequently, comprehending alterations in the viscous properties of cells can aid in establishing another cellular aging marker and better understanding the aging process. Hence, further emphasis should be placed on the measurement of cellular viscous or viscoelastic properties using established techniques such as AFM, microfluidics, or magnetic tweezers in future research.

Cellular aging is driven not only by chronological factors such as time or cell replication but also by various stressors that contribute to aging (Fig. 3a). These stressors include UV light, hydrostatic pressure, disturbed flow, drugs, smoking, and chemicals, among others

[73]. Early findings have revealed significant differences in molecular or biochemical properties between natural aging and stressor-induced aging [74]. For instance, cell cycle arrest and telomere shortening are prominent features in naturally aging cells, whereas they may not be present in cells undergoing stress-induced aging. Furthermore, it has been observed that cells undergoing aging induced by stressors such as disturbed flow or cancer therapy secrete a much higher level of senescence-associated secretory phenotype (SASP) factors, including excessive reactive oxygen species (ROS), compared to naturally aging cells [74]. These findings suggest that the pattern of changes in mechanical properties may vary depending on the type of factors contributing to aging. Therefore, in future studies, it is essential to consider how the type of aging-causing factors influences changes in mechanical or viscoelastic properties.

One of the limitations is that the majority of the measurements have been conducted at room temperature, which lacks physiological relevance. Therefore, exploring changes in cellular mechanical properties within physiologically relevant environments can narrow the gap between *in vitro* and *in vivo* mechanical properties, thereby offering deeper insights into aging physiology and biological mechanisms [21].

4. Conclusion

Aging induces significant alterations in the structural, mechanical, and biochemical properties of cells. Among these changes, mechanical characteristics such as elastic and viscoelastic properties play a pivotal role, serving as indicators of both physiological and pathological conditions as well as the aging process itself. Various techniques have been employed to investigate aging-related mechanical changes at the cellular level. Studies have demonstrated notable differences between aging cells, including erythrocytes, leukocytes, ECs, cardiomyocytes, osteocytes, and epithelial cells, when compared to their younger counterparts. Thus, comprehending the mechanical alterations associated with aging across different cell types holds promise in identifying markers for aging and understanding how different therapies, including vaccination, cell therapy, and gene therapy, will work for the aged population. Furthermore, linking these changes in mechanical properties with alterations in biochemical and structural properties will further advance our understanding of aging biology.

Data availability statement

Data will be made available upon request.

CRediT authorship contribution statement

Amarnath Singam: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Chandrabali Bhattacharya:** Writing – review & editing. **Seungman Park:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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References

[1] S. Park, W.H. Jung, M. Pittman, J. Chen, Y. Chen, The effects of stiffness, fluid viscosity, and geometry of microenvironment in homeostasis, aging, and diseases: a brief review, J. Biomech. Eng. (2020), https://doi.org/10.1115/1.4048110.
[2] S. Park, Biochemical, structural and physical changes in aging human skin, and their relationship, Biogerontology 23 (2022) 275–288, https://doi.org/10.1007/s10522-022-09959-w.
[3] T.M.J. Evers, L.J. Holt, S. Alberti, A. Mashaghi, Reciprocal regulation of cellular mechanics and metabolism, Nat. Metab. 3 (2021) 456–468, https://doi.org/10.1038/s42255-021-00384-w.
[4] A.K. Palmer, M.D. Jensen, Metabolic changes in aging humans: current evidence and therapeutic strategies, J. Clin. Invest. 132 (2022), https://doi.org/10.1172/JCI158451.
[5] D. Guan, Y. Shen, R. Zhang, P. Huang, P.-Y. Lai, P. Tong, Unified description of compressive modulus revealing multiscale mechanics of living cells, Phys. Rev. Res. 3 (2021) 043166, https://doi.org/10.1103/PhysRevResearch.3.043166.
[6] P.-H. Wu, S.S. Gambhir, C.M. Hale, W.-C. Chen, D. Wirtz, B.R. Smith, Particle tracking microrheology of cancer cells in living subjects, Mater. Today 39 (2020) 98–109, https://doi.org/10.1016/j.mattod.2020.03.021.
[7] M.S. Yousafzai, F. Ndoye, G. Coceano, J. Niemela, S. Bonin, G. Scoles, D. Cojoc, Substrate-dependent cell elasticity measured by optical tweezers indentation, Opt Laser. Eng. 76 (2016) 27–33, https://doi.org/10.1016/j.optlaseng.2015.02.008.
[8] C.T. Mierke, T. Fischer, S. Puder, T. Kunschmann, B. Soetje, W.H. Ziegler, Focal adhesion kinase activity is required for actomyosin contractility-based invasion of cells into dense 3D matrices, Sci. Rep. 7 (2017) 42780, https://doi.org/10.1038/srep42780.
[9] S. Park, Y.K. Joo, Y. Chen, Versatile and high-throughput force measurement platform for dorsal cell mechanics, Sci. Rep. 9 (2019) 13286, https://doi.org/10.1038/s41598-019-49592-1.

[10] J. Lam, M. Herant, M. Dembo, V. Heinrich, Baseline mechanical characterization of J774 macrophages, Biophys. J. 96 (2009) 248–254, https://doi.org/10.1529/biophysj.108.139154.

[11] Q. Luo, D. Kuang, B. Zhang, G. Song, Cell stiffness determined by atomic force microscopy and its correlation with cell motility, Biochim. Biophys. Acta Gen. Subj. 1860 (2016) 1953–1960, https://doi.org/10.1016/j.bbagen.2016.06.010.

[12] T.G. Kuznetsova, M.N. Starodubtseva, N.I. Yegorenkov, S.A. Chizhik, R.I. Zhdanov, Atomic force microscopy probing of cell elasticity, Micron 38 (2007) 824–833, https://doi.org/10.1016/j.micron.2007.06.011.

[13] D. Wirtz, Particle-tracking microrheology of living cells: principles and applications, Annu. Rev. Biophys. 38 (2009) 301–326, https://doi.org/10.1146/annurev.biophys.050708.133724.

[14] A.R. Bausch, W. Möller, E. Sackmann, Measurement of local viscoelasticity and forces in living cells by magnetic tweezers, Biophys. J. 76 (1999) 573–579, https://doi.org/10.1016/S0006-3495(99)77225-5.

[15] C. Gosse, V. Croquette, Magnetic tweezers: micromanipulation and force measurement at the molecular level, Biophys. J. 82 (2002) 3314–3329, https://doi.org/10.1016/S0006-3495(02)75672-5.

[16] A.R. Bausch, F. Ziemann, A.A. Boulbitch, K. Jacobson, E. Sackmann, Local measurements of viscoelastic parameters of adherent cell surfaces by magnetic bead microrheometry, Biophys. J. 75 (1998) 2038–2049.

[17] Z. Chen, Y. Zhu, D. Xu, MdM. Alam, L. Shui, H. Chen, Cell elasticity measurement using a microfluidic device with real-time pressure feedback, Lab Chip 20 (2020) 2343–2353, https://doi.org/10.1039/D0LC00092B.

[18] B. González-Bermúdez, G.V. Guinea, G.R. Plaza, Advances in micropipette aspiration: applications in cell biomechanics, models, and extended studies, Biophys. J. 116 (2019) 587–594, https://doi.org/10.1016/j.bpj.2019.01.004.

[19] M.-J. Oh, F. Kuhr, F. Byfield, I. Levitan, Micropipette aspiration of substrate-attached cells to estimate cell stiffness, JoVE (2012), https://doi.org/10.3791/3886.

[20] Y. Hao, S. Cheng, Y. Tanaka, Y. Hosokawa, Y. Yalikun, M. Li, Mechanical properties of single cells: measurement methods and applications, Biotechnol. Adv. 45 (2020) 107648, https://doi.org/10.1016/j.biotechadv.2020.107648.

[21] T.M.J. Evers, A. van Weverwijk, K.E. de Visser, A. Mashaghi, Single-cell analysis of innate immune cell mechanics: an application to cancer immunology, Mater Adv (2024), https://doi.org/10.1039/D3MA01107K.

[22] J.M. Phillip, I. Aifuwa, J. Walston, D. Wirtz, The mechanobiology of aging, Annu. Rev. Biomed. Eng. 17 (2015) 113–141, https://doi.org/10.1146/annurev-bioeng-071114-040829.

[23] T.G. Kuznetsova, M.N. Starodubtseva, N.I. Yegorenkov, S.A. Chizhik, R.I. Zhdanov, Atomic force microscopy probing of cell elasticity, Micron 38 (2007) 824–833, https://doi.org/10.1016/j.micron.2007.06.011.

[24] Z. Su, Z. Chen, K. Ma, H. Chen, J.W.K. Ho, Molecular determinants of intrinsic cellular stiffness in health and disease, Biophys Rev 14 (2022) 1197–1209, https://doi.org/10.1007/s12551-022-00997-9.

[25] C.-H. Hsieh, Y.-H. Lin, S. Lin, J.-J. Tsai-Wu, C.H. Herbert Wu, C.-C. Jiang, Surface ultrastructure and mechanical property of human chondrocyte revealed by atomic force microscopy, Osteoarthritis Cartilage 16 (2008) 480–488, https://doi.org/10.1016/j.joca.2007.08.004.

[26] M. Depond, B. Henry, P. Buffet, P.A. Ndour, Methods to investigate the deformability of RBC during malaria, Front. Physiol. 10 (2020), https://doi.org/10.3389/fphys.2019.01613.

[27] S.M. Hosseini, J.J. Feng, How malaria parasites reduce the deformability of infected red blood cells, Biophys. J. 103 (2012) 1–10, https://doi.org/10.1016/j.bpj.2012.05.026.

[28] M.L. Ellsworth, C.G. Ellis, D. Goldman, A.H. Stephenson, H.H. Dietrich, R.S. Sprague, Erythrocytes: oxygen sensors and modulators of vascular tone, Physiology 24 (2009) 107–116, https://doi.org/10.1152/physiol.00038.2008.

[29] M.N. Starodubtseva, Mechanical properties of cells and ageing, Ageing Res. Rev. 10 (2011) 16–25, https://doi.org/10.1016/j.arr.2009.10.005.

[30] M. Baumann, Cell ageing for 1 day alters both membrane elasticity and viscosity, Pflugers Arch 445 (2003) 551–555, https://doi.org/10.1007/s00424-002-0979-6.

[31] T. Böhler, A. Leo, A. Stadler, O. Linderkamp, Mechanical fragility of erythrocyte membrane in neonates and adults, Pediatr. Res. 32 (1992) 92–96, https://doi.org/10.1203/00006450-199207000-00018.

[32] F.H. Bosch, J.M. Werre, L. Schipper, B. Roerdinkholder-Stoelwinder, T. Huls, F.L.A. Willekens, G. Wichers, M.R. Halie, Determinants of red blood cell deformability in relation to cell age, Eur. J. Haematol. 52 (1994) 35–41, https://doi.org/10.1111/j.1600-0609.1994.tb01282.x.

[33] Y. Marikovsky, The cytoskeleton in ATP-depleted erythrocytes: the effect of shape transformation, Mech. Ageing Dev. 86 (1996) 137–144, https://doi.org/10.1016/0047-6374(95)01683-X.

[34] F. Liu, H. Mizukami, S. Sarnaik, A. Ostafin, Calcium-dependent human erythrocyte cytoskeleton stability analysis through atomic force microscopy, J. Struct. Biol. 150 (2005) 200–210, https://doi.org/10.1016/j.jsb.2005.02.001.

[35] M.N. Starodubtseva, T.G. Kuznetsova, S.N. Cherenkevich, Effect of peroxynitrite on mechanical properties of human erythrocyte membranes, Bull. Exp. Biol. Med. 143 (2007) 264–267, https://doi.org/10.1007/s10517-007-0066-2.

[36] M.N. Starodubtseva, A.L. Tattersall, T.G. Kuznetsova, N.I. Yegorenkov, J.C. Ellory, Structural and functional changes in the membrane and membrane skeleton of red blood cells induced by peroxynitrite, Bioelectrochemistry 73 (2008) 155–162, https://doi.org/10.1016/j.bioelechem.2008.01.008.

[37] C. Schulze, F. Wetzel, T. Kueper, A. Malsen, G. Muhr, S. Jaspers, T. Blatt, K.-P. Wittern, H. Wenck, J.A. Käs, Stiffening of human skin fibroblasts with age, Biophys. J. 99 (2010) 2434–2442, https://doi.org/10.1016/j.bpj.2010.08.026.

[38] P. Friedl, B. Weigelin, Interstitial leukocyte migration and immune function, Nat. Immunol. 9 (2008) 960–969, https://doi.org/10.1038/ni.f.212.

[39] B. González-Bermúdez, H. Kobayashi, A. Abarca-Ortega, M. Córcoles-Lucas, M. González-Sánchez, M. De la Fuente, G.V. Guinea, M. Elices, G.R. Plaza, Aging is accompanied by T-cell stiffening and reduced interstitial migration through dysfunctional nuclear organization, Immunology 167 (2022) 622–639, https://doi.org/10.1111/imm.13559.

[40] E.S. White, Lung extracellular matrix and fibroblast function, Ann Am Thorac Soc 12 (2015) S30–S33, https://doi.org/10.1513/AnnalsATS.201406-240MG.

[41] I. Dulińska-Molak, M. Pasikowska, K. Pogoda, M. Lewandowska, I. Eris, M. Lekka, Age-related changes in the mechanical properties of human fibroblasts and its prospective reversal after anti-wrinkle tripeptide treatment, Int J Pept Res Ther 20 (2014) 77–85, https://doi.org/10.1007/s10989-013-9370-z.

[42] J.T. Zahn, I. Louban, S. Jungbauer, M. Bissinger, D. Kaufmann, R. Kemkemer, J.P. Spatz, Age-Dependent changes in microscale stiffness and mechanoresponses of cells, Small 7 (2011) 1480–1487, https://doi.org/10.1002/smll.201100146.

[43] C. Michiels, Endothelial cell functions, J. Cell. Physiol. 196 (2003) 430–443, https://doi.org/10.1002/jcp.10333.

[44] J.A. Chouinard, G. Grenier, A. Khalil, P. Vermette, Oxidized-LDL induce morphological changes and increase stiffness of endothelial cells, Exp. Cell Res. 314 (2008) 3007–3016, https://doi.org/10.1016/j.yexcr.2008.07.020.

[45] M. Sato, K. Suzuki, Y. Ueki, T. Ohashi, Microelastic mapping of living endothelial cells exposed to shear stress in relation to three-dimensional distribution of actin filaments, Acta Biomater. 3 (2007) 311–319, https://doi.org/10.1016/j.actbio.2006.07.009.

[46] M. Li, N.K. Fukagawa, Age-related changes in redox signaling and VSMC function, Antioxid Redox Signal 12 (2010) 641–655, https://doi.org/10.1089/ars.2009.2854.

[47] W. Zhu, B.C. Kim, M. Wang, J. Huang, A. Isak, N.M. Bexiga, R. Monticone, T. Ha, E.G. Lakatta, S.S. An, TGFβ1 reinforces arterial aging in the vascular smooth muscle cell through a long-range regulation of the cytoskeletal stiffness, Sci. Rep. 8 (2018) 2668, https://doi.org/10.1038/s41598-018-20763-w.

[48] H. Qiu, Y. Zhu, Z. Sun, J.P. Trzeciakowski, M. Gansner, C. Depre, R.R.G. Resuello, F.F. Natividad, W.C. Hunter, G.M. Genin, E.L. Elson, D.E. Vatner, G. A. Meininger, S.F. Vatner, Short communication: vascular smooth muscle cell stiffness as a mechanism for increased aortic stiffness with aging, Circ. Res. 107 (2010) 615–619, https://doi.org/10.1161/CIRCRESAHA.110.221846.

[49] J.W. Seawright, H. Sreenivasappa, H.C. Gibbs, S. Padgham, S.Y. Shin, C. Chaponnier, A.T. Yeh, J.P. Trzeciakowski, C.R. Woodman, A. Trache, Vascular smooth muscle contractile function declines with age in skeletal muscle feed arteries, Front. Physiol. 9 (2018), https://doi.org/10.3389/fphys.2018.00856.

[50] D. Sicard, A.J. Haak, K.M. Choi, A.R. Craig, L.E. Fredenburgh, D.J. Tschumperlin, Aging and anatomical variations in lung tissue stiffness, Am. J. Physiol. Lung Cell Mol. Physiol. 314 (2018) L946–L955, https://doi.org/10.1152/ajplung.00415.2017.
[51] D. Bernhard, G. Laufer, The aging cardiomyocyte: a mini-review, Gerontology 54 (2008) 24–31, https://doi.org/10.1159/000113503.
[52] S.C. Lieber, H. Qiu, L. Chen, Y.-T. Shen, C. Hong, W.C. Hunter, N. Aubry, S.F. Vatner, D.E. Vatner, Cardiac dysfunction in aging conscious rats: altered cardiac cytoskeletal proteins as a potential mechanism, Am. J. Physiol. Heart Circ. Physiol. 295 (2008) H860–H866, https://doi.org/10.1152/ajpheart.00146.2008.
[53] S.C. Lieber, N. Aubry, J. Pain, G. Diaz, S.-J. Kim, S.F. Vatner, Aging increases stiffness of cardiac myocytes measured by atomic force microscopy nanoindentation, Am. J. Physiol. Heart Circ. Physiol. 287 (2004) H645–H651, https://doi.org/10.1152/ajpheart.00564.2003.
[54] D.M. Findlay, G.J. Atkins, Osteoblast-Chondrocyte interactions in osteoarthritis, Curr. Osteoporos. Rep. 12 (2014) 127–134, https://doi.org/10.1007/s11914-014-0192-5.
[55] N. Steklov, A. Srivastava, K.L.P. Sung, P.C. Chen, M.K. Lotz, D.D. D'Lima, Aging-related differences in chondrocyte viscoelastic properties, Mol. Cell. BioMech. 6 (2009) 113–119.
[56] N.O. Chahine, C. Blanchette, C.B. Thomas, J. Lu, D. Haudenschild, G.G. Loots, Effect of age and cytoskeletal elements on the indentation-dependent mechanical properties of chondrocytes, PLoS One 8 (2013) e61651, https://doi.org/10.1371/journal.pone.0061651.
[57] B.N.G. Giepmans, S.C.D. van Ijzendoorn, Epithelial cell–cell junctions and plasma membrane domains, Biochim. Biophys. Acta Biomembr. 1788 (2009) 820–831, https://doi.org/10.1016/j.bbamem.2008.07.015.
[58] T.K. Berdyyeva, C.D. Woodworth, I. Sokolov, Human epithelial cells increase their rigidity with ageing *in vitro* : direct measurements, Phys. Med. Biol. 50 (2005) 81–92, https://doi.org/10.1088/0031-9155/50/1/007.
[59] I. Sokolov, S. Iyer, C.D. Woodworth, Recovery of elasticity of aged human epithelial cells in vitro, Nanomedicine 2 (2006) 31–36, https://doi.org/10.1016/j.nano.2005.12.002.
[60] J. Ochala, W.R. Frontera, D.J. Dorer, J.V. Hoecke, L.S. Krivickas, Single skeletal muscle fiber elastic and contractile characteristics in young and older men, J Gerontol A Biol Sci Med Sci 62 (2007) 375–381, https://doi.org/10.1093/gerona/62.4.375.
[61] S. Kiderlen, C. Polzer, J.O. Rädler, D. Docheva, H. Clausen-Schaumann, S. Sudhop, Age related changes in cell stiffness of tendon stem/progenitor cells and a rejuvenating effect of ROCK-inhibition, Biochem. Biophys. Res. Commun. 509 (2019) 839–844, https://doi.org/10.1016/j.bbrc.2019.01.027.
[62] Y. Zhu, H. Qiu, J.P. Trzeciakowski, Z. Sun, Z. Li, Z. Hong, M.A. Hill, W.C. Hunter, D.E. Vatner, S.F. Vatner, G.A. Meininger, Temporal analysis of vascular smooth muscle cell elasticity and adhesion reveals oscillation waveforms that differ with aging, Aging Cell 11 (2012) 741–750, https://doi.org/10.1111/j.1474-9726.2012.00840.x.
[63] K.S. Kim, H.-K. Park, J.-W. Lee, Y. Il Kim, M.K. Shin, Investigate correlation between mechanical property and aging biomarker in passaged human dermal fibroblasts, Microsc. Res. Tech. 78 (2015) 277–282, https://doi.org/10.1002/jemt.22472.
[64] M.N. Starodubtseva, A.L. Tattersall, T.G. Kuznetsova, N.I. Yegorenkov, J.C. Ellory, Structural and functional changes in the membrane and membrane skeleton of red blood cells induced by peroxynitrite, Bioelectrochemistry 73 (2008) 155–162, https://doi.org/10.1016/j.bioelechem.2008.01.008.
[65] K.M.K. Rao, M.S. Currie, J. Padmanabhan, H.J. Cohen, Age-related alterations in actin cytoskeleton and receptor expression in human leukocytes, J. Gerontol. 47 (1992) B37–B44, https://doi.org/10.1093/geronj/47.2.B37.
[66] A.C. Flor, D. Wolfgeher, D. Wu, S.J. Kron, A signature of enhanced lipid metabolism, lipid peroxidation and aldehyde stress in therapy-induced senescence, Cell Death Discov 3 (2017) 17075, https://doi.org/10.1038/cddiscovery.2017.75.
[67] J.-T. Hang, Y. Kang, G.-K. Xu, H. Gao, A hierarchical cellular structural model to unravel the universal power-law rheological behavior of living cells, Nat. Commun. 12 (2021) 6067, https://doi.org/10.1038/s41467-021-26283-y.
[68] B. Corominas-Murtra, N.I. Petridou, Viscoelastic networks: forming cells and tissues, Front Phys 9 (2021), https://doi.org/10.3389/fphy.2021.666916.
[69] W. Trickey, T. Vail, F. Guilak, The role of the cytoskeleton in the viscoelastic properties of human articular chondrocytes, J. Orthop. Res. 22 (2004) 131–139, https://doi.org/10.1016/S0736-0266(03)00150-5.
[70] K. Yu, Y. Jiang, Y. Chen, X. Hu, J. Chang, G.V. Hartland, G.P. Wang, Compressible viscoelasticity of cell membranes determined by gigahertz-frequency acoustic vibrations, Photoacoustics 31 (2023) 100494, https://doi.org/10.1016/j.pacs.2023.100494.
[71] J. Xie, J. Najafi, R. Le Borgne, J.-M. Verbavatz, C. Durieu, J. Sallé, N. Minc, Contribution of cytoplasm viscoelastic properties to mitotic spindle positioning, Proc. Natl. Acad. Sci. USA 119 (2022), https://doi.org/10.1073/pnas.2115593119.
[72] S. Phuyal, P. Romani, S. Dupont, H. Farhan, Mechanobiology of organelles: illuminating their roles in mechanosensing and mechanotransduction, Trends Cell Biol. 33 (2023) 1049–1061, https://doi.org/10.1016/j.tcb.2023.05.001.
[73] S. Park, T.C. Laskow, J. Chen, P. Guha, B. Dawn, D. Kim, Microphysiological systems for human aging research, Aging Cell (2024), https://doi.org/10.1111/acel.14070.
[74] A. Dominic, P. Banerjee, D.J. Hamilton, N.T. Le, J. ichi Abe, Time-dependent replicative senescence vs. disturbed flow-induced pre-mature aging in atherosclerosis, Redox Biol. 37 (2020), https://doi.org/10.1016/j.redox.2020.101614.