High stretchability, strength, and toughness of living cells enabled by hyperelastic vimentin intermediate filaments

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Edited by Jennifer Lippincott-Schwartz, Janelia Farm Research Campus, Ashburn, VA, and approved July 23, 2019 (received for review March 6, 2019)

In many developmental and pathological processes, including cellular migration during normal development and invasion in cancer metastasis, cells are required to withstand severe deformations. The structural integrity of eukaryotic cells under small deformations has been known to depend on the cytoskeleton including actin filaments (F-actin), microtubules (MT), and intermediate filaments (IFs). However, it remains unclear how cells resist severe deformations since both F-actin and microtubules yield or disassemble under moderate strains. Using vimentin containing IFs (VIFs) as a model for studying the large family of IF proteins, we demonstrate that they dominate cytoplasmic mechanics and maintain cell viability at large deformations. Our results show that cytoskeletal VIFs form a stretchable, hyperelastic network in living cells. This network works synergistically with other cytoplasmic components, substantially enhancing the strength, stretchability, resilience, and toughness of cells. Moreover, we find the hyperelastic VIF network, together with other quickly recoverable cytoskeletal components, forms a mechanically robust structure which can mechanically recover after damage.

vimentin | intermediate filament | cytoskeleton | cytoplasm | cell mechanics

Mesenchymal cells such as fibroblasts play central roles in many physiological processes including the epithelial to mesenchymal transition (EMT) that takes place during normal embryonic development, in cancer metastasis, and in wound healing (1, 2). During these physiological processes, mesenchymal cells experience severe deformations as they engage in the migratory and invasive activities associated with these processes (3), highlighting the importance for cells to maintain mechanical integrity under large deformations. Recent studies have emphasized the importance of nuclear envelope rupture and repair mechanisms in limiting DNA damage during mechanical stress (4, 5). In contrast, the mechanisms involved in protecting the remaining cytoplasm and its constituent organelles against severe deformations remain unclear.

The ability of eukaryotic cells to resist deformation depends on the cytoskeleton, an interconnected network of biopolymers including F-actin, MT, and IFs (6). Previous *in vitro* work has demonstrated that both F-actin and MT structures yield or disassemble at moderate strains (20 and 60%, respectively) (7), suggesting that they cannot maintain the mechanical integrity and resilience of the cytoplasm at the even larger strains which take place in the physiological processes mentioned above. Therefore, it has been hypothesized that cytoplasmic IFs may play an important role in maintaining the mechanical integrity and resilience of cells, especially under large deformations (8, 9). As a key phenotypic marker of mesenchymal cells, vimentin IFs (VIFs) are known to be critical for regulating cell shape, migration (10), and cytoplasmic stiffness at small deformations (11,

12). However, their structural and mechanical roles in living mesenchymal cells at large deformations remain unknown.

Here we show that VIFs behave as a strain-stiffening hyperelastic network in mesenchymal cells and that they determine cellular strength, stretchability, resilience, and toughness. VIF networks interconnect with other cytoskeletal networks and effectively disperse local deformations in the cytoplasm, and thus lead to a significant increase in the mechanical energy input required to damage the cytoplasm. Furthermore, the hyperelastic VIF network can dramatically slow down both poroelastic relaxation and viscoelastic relaxation processes in the cytoplasm, which can enhance the mechanical damping capability of the cytoplasm and thus protect organelles against mechanical damage. Our results provide a fundamental insight into the role of cytoskeletal IFs in the maintenance of cell structure, mechanical integrity, and resilience during a variety of key physiological processes.

Results

VIF Networks Dominate Cytoplasmic Mechanics and Maintain Cell Viability under Large Deformations. To study the effect of VIFs in cytoplasmic mechanics, we use wild-type (WT) and vimentin

Significance

Intermediate filaments (IFs) remain the least understood with respect to their functions in mammalian cells even though they have been related to many devastating human diseases. Here we use optical tweezers to perform micromechanical measurements in living cells and in IF enriched cytoskeletons devoid of actin and microtubules. We identify that cytoskeletal vimentin IFs (VIFs) provide cells with a hyperelastic rubber-like network that regulates the essential mechanical properties of mammalian cells including stretchability, strength, resilience, and toughness. We show that VIFs maintain cell integrity and viability under conditions involving extreme deformations. We further show that the stretchy VIF network can effectively disperse locally induced mechanical stress to larger regions within individual cells, enabling the dissipation of energy throughout a cell.

Author contributions: J.H. and M.G. designed research; J.H., Y.L., Y.H., and T.Z. performed research; Y.L., Y.H., T.Z., S.K.G., G.A.P., H.W., S.L., X.Z., R.D.G., and S.C. contributed new reagents/analytic tools; J.H., Y.L., Y.H., and S.W. analyzed data; M.G. supervised the project; and J.H., R.D.G., S.C., and M.G. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1903890116/-DCSupplemental.

Published online August 13, 2019.

The relaxed normalized force (relaxed F/S) is higher in the WT mEFs (25.4 ± 9.2 Pa) than that in the $Vim^{-/-}$ mEFs (14.7 ± 4.6 Pa), as shown in Fig. 2B. Interestingly, the presence of VIFs markedly increases the poroelastic relaxation time in cells; we find that $t_p = 0.042 \pm 0.008$ s in the WT mEFs and 0.033 ± 0.005 s in the $Vim^{-/-}$ mEFs (Fig. 2C, *Inset*). This suggests that VIFs reduce the average cytoplasmic mesh size. Moreover, as we fit the relaxation curves at long time scales ($t > 0.1$ s, as shown in Fig. 2C) to a power law function (23, 24), $F/S \sim t^{-\beta}$, to characterize the viscoelastic relaxation speed of the cytoplasm, we find a lower relaxation speed ($\beta = 0.25 \pm 0.04$) in the WT mEFs compared to the $Vim^{-/-}$ mEFs ($\beta = 0.31 \pm 0.03$). This might be due to friction and other interactions between VIF networks and other cytoskeletal components. Consistently, both the relaxation time and the relaxed force further increase in living mEFs with VIFs overexpressed (OverE), as shown in Fig. 2C. The increased relaxed force and relaxation times in the WT and OverE mEFs, compared with the $Vim^{-/-}$ mEFs, imply that VIF networks can regulate the mechanical damping capacity of the cytoplasm and thereby provide an optimal protection against mechanical stress and damage for organelles while maintaining the structural integrity of cells.

The relaxation test results indicate that VIF networks remain elastic up to deformations of $X/a = 0.4$. To study the yielding strain (the strain limit after which the material exhibits a plastic response) of VIF networks in living cells, we apply different deformations ($X/a = 0.4$ to 1.2) by dragging a $1\text{-}\mu\text{m}$ -diameter bead at $1\text{ }\mu\text{m/s}$ using optical tweezers. After reaching the expected initial displacement, we release the force applied on the bead by turning off the laser power, subsequently recording the movement of the released bead by microscopic imaging. After releasing the loading force, the bead moves backward with time (Fig. 2D–F), indicating an elastic recovery of the cytoplasmic deformation. We find that there is full recovery of deformations up to $X/a = 0.8$ in WT mEFs, while the $Vim^{-/-}$ mEFs begin to exhibit plastic deformation (i.e., not fully recovered) for deformations X/a below 0.4 . This result shows that VIF networks can increase the yielding strain and thus the resilience of the cytoplasm, providing living cells with a mechanism for recovering their original shapes and structures after large deformations.

Hyperelastic VIF Networks Regulate the Toughness of the Cytoplasm by Increasing Both Dissipated Energy and Elastic Energy under Loading. The capacity of energy absorption is an important parameter characterizing materials; it can be quantified using the material's toughness, obtained by calculating the extension work via integrating the stress–strain curve (25). To determine this parameter in cells and to further define the functions of VIF, we have integrated the normalized force–displacement curve to $X/a = 1.2$ to obtain the extension work of cells (Fig. 1I). We find that the extension work is larger in the WT mEFs than the sum of those in the $Vim^{-/-}$ mEFs and the VIF ghost cell (*SI Appendix, Fig. S8*). Since we locally deform the cytoplasm using a bead, complete fracture of the cytoplasm is not achieved at the end of the loading; nevertheless, this comparison suggests that the cytoplasmic toughness of the WT mEFs is greater than the superposition of the $Vim^{-/-}$ mEFs and the VIF ghost cell, indicating a direct interaction between VIFs and the rest of the cytoplasmic components.

To further investigate the underlying mechanisms by which VIFs enhance the toughness and resilience of the cytoplasm, cyclic loading and unloading tests are carried out in cells (Fig. 3A, *Inset*). This test quantifies both the elastic and dissipated mechanical energy that together constitute material toughness. Surprisingly, the loading and unloading curves obtained in the VIF ghost cell collapse and remain unchanged over more than 100 cycles (Fig. 3A). This result further demonstrates that the cytoplasmic VIF network itself is hyperelastic and with negligible

Fig. 3. The VIF network increases the toughness of the cytoplasm by increasing dissipated energy and elastic energy. (A) Cyclic loading in the cell is achieved by reciprocating movement of a bead at a speed of $1\text{ }\mu\text{m/s}$ using optical tweezers (*Inset*). The first and 100th loading and unloading curves in VIF ghost cells overlap. The semitransparent band around the average curves represents the SE ($n = 15$ cells). (B and C) Plot of the first and 10th cyclic loading curves in WT mEFs (B) and $Vim^{-/-}$ mEFs (C). After being damaged by repeated loadings, the loading curves in both WT and $Vim^{-/-}$ mEFs recover to original levels in 10 min, highlighting the self-healing nature of the cytoplasm. The semitransparent band around the average curves represents the SE ($n = 20$ cells for each curve). See full curves in *SI Appendix, Fig. S10*. (D) VIF ghost cell does not dissipate energy. WT mEFs have significantly higher extension work, dissipated energy, and elastic energy than $Vim^{-/-}$ mEFs. Error bars represent SD ($n = 15$ cells for ghost cells, $n = 20$ cells for WT and $Vim^{-/-}$ mEFs). ns, not significant; *** $P < 0.001$.

energy dissipation (Fig. 3D). Individual VIFs have been shown to be capable of dissipating mechanical energy due to unfolding of α helices under stretch on single filaments (26–28); our results suggest that before individual filaments reaching this unfolding state, the VIF networks could globally retain an elastic regime under moderate to large deformations. When this measurement is made in the WT mEFs, a clear hysteresis loop is observed, suggesting energy is being dissipated during this process (Fig. 3B and *SI Appendix, Fig. S10*). Furthermore, the cytoplasm is greatly softened over the first 3 cycles and eventually becomes similar to that measured in the ghost cell after 10 cycles (Fig. 2B and *SI Appendix, Fig. S10*). In contrast, the resistant force in the $Vim^{-/-}$ mEFs eventually becomes very weak (Fig. 3C), suggesting that cyclic loading causes most cytoskeletal structures to be damaged, disassembled, or rearranged in cells without VIFs. After repeated cyclic loading, the normalized force–displacement curve reaches a steady state at the 10th cycle in both WT and $Vim^{-/-}$ mEFs; integration of the steady-state force–displacement curve represents the elastic energy of the cytoplasm. These results show that elastic energy is significantly higher in the WT mEFs as compared to the $Vim^{-/-}$ mEFs (Fig. 3D), further suggesting that the VIF network maintains the resilience of the cytoplasm during cyclic loading, while the rest of the cytoplasmic components (such as F-actin and microtubules) contribute to the energy dissipation. To further quantify the energy dissipation, we integrate the area looped by the first loading and unloading curves (Fig. 3A–C). We find that the dissipated energy density is significantly higher in the WT mEFs than in the $Vim^{-/-}$ mEFs (Fig. 3D), demonstrating that the existence of the VIF network can also substantially increase the energy dissipated by the cytoplasm. Since the VIF network itself is hyperelastic and

does not dissipate mechanical energy (Fig. 3D), the observed enhancement in energy dissipation is more likely due to other cellular components (F-actin, MTs, and cytosol) through their interactions with VIFs. Therefore, the stretchy elastic VIF network and the other dissipative cytoplasmic components work synergistically, enhancing cytoplasmic toughness. Indeed, the VIF network interpenetrates with other cytoskeletal networks as shown in previous literature (29, 30), providing an unavoidable physical interaction between different networks.

Our results show that VIFs are essential for the cytoplasm to retain high strength, stretchability, and toughness under frequent large deformations, thus preventing the cytoplasm from becoming irreversibly damaged during important cell migratory and invasive activities. Interestingly, we also find that the living cytoplasm shows significant softening after repeated loading but can recover to its original state after a 10-min rest (Fig. 3B and C). This likely reflects the rapid self-reorganizing ability of other cytoskeletal structures, as also observed in both mechanical testing and microscopic imaging of reconstituted actin and microtubule networks (31–34), even though these 2 cytoskeletal structures are easily disassociated upon initial loading. Such mechanically recovering after damage observed in the living cell cytoplasm is substantially more efficient than in typical artificial materials (35).

Hyperelastic VIF Networks Extend the Cytoplasmic Deformation Field under Localized Loading. To further understand the mechanisms by which VIFs enhance and regulate the mechanical properties of cytoplasm and increase the dissipated mechanical energy of the cytoplasm, we image the resultant displacement and strain fields upon introducing a local deformation in the cytoplasm. We drag a 2- μm -diameter bead in the cytoplasm over 200 nm at a speed of 2 $\mu\text{m/s}$ and perform particle image velocimetry by visualizing 2D projected movements of surrounding fluorescently labeled mitochondria (Fig. 4A and B). We find that the deformation field extends significantly farther in the WT mEFs than in the *Vim*^{−/−} mEFs (Fig. 4C and D and [Movies S2](#) and [S3](#)). To quantify this effect, we plot the local cytoplasmic displacement as a function of the distance to the loading center along the drag direction (white dashed lines in Fig. 4C and D), where the

displacement (U) is normalized by the bead displacement (U_0), and the distance (X) is normalized by the bead radius (R), as shown in Fig. 4G. The normalized displacement decays with normalized distance as a power law with a power of -1 in the cytoplasm of the WT mEFs. In contrast, the observed displacement decay is markedly faster in the *Vim*^{−/−} mEFs (Fig. 4G) with a power of -2 . Consistently, the normal strain field computed from the 2D displacement map concentrates around the loading point in the *Vim*^{−/−} mEFs while it extends significantly farther in the WT mEFs (Fig. 4E and F and [SI Appendix, Fig. S11](#)). To further show that VIFs dominate the deformation fields, we perform this measurement in VIF overexpression mEFs ([SI Appendix, Fig. S7](#)) and WT mEFs with F-actin and MTs depolymerized ([SI Appendix, Fig. S6](#)); we do not observe any statistically significant difference in the deformation field in either of these cells, as compared to the control WT mEFs. Taken together, these results demonstrate the important contribution of VIF networks in increasing the propagation of local deformations in the cytoplasm, therefore involving more cytoplasmic materials to deform under to local loading.

Other cytoskeletal components such as F-actin and microtubules are easily relaxed and reorganized under deformation, as shown by both our measurements in cells (Fig. 24) and macroscopic rheology measurements of reconstituted networks (21); once relaxed and reorganized, they quickly lose the ability to transmit stress and strain. However, the high stretchability and hyperelastic nature of the VIF network allows it to maintain structural and mechanical integrity under very large strains (more than 300%), therefore enabling local strain and stress to be effectively transmitted from a stress concentrated area to a larger zone in the cell (Fig. 4H). As widely observed in common materials, stress/strain concentrations are the major cause of material damage (36). Under a concentrated loading, the stretchy, hyperelastic VIF network not only stores substantial mechanical energy by itself but also increases the dissipated mechanical energy significantly by deforming larger volumes of the cytoplasm near the stress concentration. Therefore, the presence of such an interconnected VIF network can markedly increase the required mechanical energy to damage the cytoplasm under the same loading force.

Fig. 4. VIFs extend the cytoplasmic deformation field under local loading, acting as a stretchable hyperelastic network. (A and B) Deformation field is obtained by dragging a 2- μm -diameter bead in the cytoplasm over 200 nm and visualizing the 2D projected movements of surrounding fluorescently labeled mitochondria. (C and D) The displacement fields around the loading beads (white circle) in WT and *Vim*^{−/−} mEFs (cell boundaries are marked with white dotted lines). The color and the length of arrows represent displacement magnitudes. (E and F) The normal strain fields in WT and *Vim*^{−/−} mEFs are obtained from displacement fields shown in C and D. The color represents the magnitude of normal strain. (G) Plot of the normalized cytoplasmic displacement as a function of the normalized distance to the loading center, along the drag directions (horizontal white dashed lines in C and D). Log-log plots are shown in the *Insets*. The semitransparent band around the average curves represents the SE ($n = 15$ cells for each curve). (H) Schematics to illustrate the mechanism of extending deformation fields by VIF network. Highly stretchable VIF networks maintain the elasticity of and transmit local strain through a large zone in the cytoplasm, while other cytoskeletal structures are easy to be damaged under deformation. The cytoskeletal mesh size and bead size are not in their actual proportion, just for illustration. (Scale bars: 10 μm in A and B and 2 μm in C–F.)

Discussion

This work uncovers the essential role of VIFs in cell mechanical behavior under large deformations. As a highly stretchable hyperelastic network, the cytoskeletal VIF network greatly enhances several of the most important mechanical properties of the cytoplasm: stretchability, resilience, strength, and toughness (SI Appendix, Table S1). The cytoplasmic stretchability is mainly determined by the VIF network. Subjected to repeated loadings, the VIF network plays an essential role in maintaining the resilience of the cytoplasm because of its high yielding strain, while the rest of cytoplasmic components are greatly softened or even disassembled. By interacting with other cytoskeletal systems and organelles, VIF networks significantly enhance cytoplasmic mechanical strength and toughness under dynamic deformations, through slowing poroelastic and viscoelastic relaxations. Moreover, the stretchy VIF network can effectively propagate local stress and strain into a larger region of the cell, deforming more microtubules and actin filaments which interpenetrate and interact with the VIF network (37, 38). Thus, VIFs significantly enhance the strength and toughness of the cytoplasm, reducing the risk of cell damage during processes involving large deformations. The enhancement of mechanical properties by VIFs is most likely required for mesenchymal cells to perform many physiological activities including cell migration during embryonic development, wound healing, and cancer metastasis. These properties of

the VIF networks may also shed light on the roles of other types of intermediate filament networks, as well as on the pathogenesis of the many human diseases associated with mutations in IF-encoding genes (39, 40). Furthermore, the stretchy and hyperelastic VIF network forms a dynamic yet mechanically robust cytoskeleton when combined with the dissipative and quickly recovering cytoskeletal components such as microtubules and actin filaments; such a collaborative design principle may inspire improved engineering of smart materials.

Materials and Methods

Full materials and methods are described in SI Appendix. Briefly, to investigate the mechanical property of the living mammalian cytoplasm, we deliver micrometer-sized polystyrene beads into living mouse embryonic fibroblasts through endocytosis. These beads distribute randomly inside the cell. To obtain the force–displacement curve in the cytoplasm, we use optical tweezers to trap and pull a bead unidirectionally with a constant speed (19, 41). To avoid any interactions with the mechanically distinct cell cortex and nucleus, we only use beads that are positioned greater than 1.5 μm away from the cell boundary and away from both the thin lamellar region and the nucleus (11, 16, 19).

ACKNOWLEDGMENTS. We thank P. Ronceray, Y. Zheng, and the M.G. laboratory for helpful discussions. This work is supported by National Cancer Institute Grant 1U01CA202123. S.C. acknowledges support from Hellman Fellows Fund. H.W. and R.D.G. acknowledge the support from the National Institutes of Health (Grant 2P01GM096971-06A1).

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