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RESEARCH ARTICLE

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Mechanics of leukemic T-cell

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Abstract

Cell mechanics is a factor that determines cell growth, migration, proliferation, or differentiation, as well as trafficking inside the cytoplasm and organization of organelles. Knowledge about cell mechanics is critical to gaining insight into these biological processes. Here, we used atomic force microscopy to examine the elasticity, an important parameter of cell mechanics, of non-adherent Jurkat leukemic T-cells in both interphase and mitotic phases. We found that the elasticity of an individual cell does not significantly change at interphase. When a cell starts to divide, its elasticity increases in the transition from metaphase to telophase during normal division while the cell is stiffened right after it enters mitosis during abnormal division. At the end of the division, the cell elasticity gradually returned to the value of the mother cell. These changes may originate from the changes in cell surface tension during modulating actomyosin at the cleavage furrow, redistributing cell organelles, and constricting the contractile ring to sever mother cell to form daughters. The difference in elasticity patterns suggests that there is a discrepancy in the redistribution of the cell organelles during normal and abnormal division.

KEYWORDS
cell division, cell elasticity, Jurkat T-cell, nanoindentation

1 | INTRODUCTION

Cell mechanics defines the response of cells to the mechanical forces exercised by the surrounding microenvironment, including the extracellular matrix and other cells. These forces exert continuously compressive, extensional, and shear forces on cells in vivo.[1] The deformability in response to mechanical forces of cells plays a pivotal role in the homeostasis of tissues and organs and the development of proper embryonic. The ability to resist deformation, transport intracellular cargo, and change shape during movement depends on the cytoskeleton. This is an interconnected network of various regulatory cytoplasmic proteins including myosin motors, microtubules, and actin filaments. It involves in upstream and downstream signaling pathways, acts as an interface for cellular processes, determines elasticity and local behavior of cells, and plays an important role in providing structural support to maintain cell shape and facilitate cell movement.[2,3] As a cell enters mitosis, the creation of the mitotic spindle and the contractile ring during nuclear and cytoplasmic division requires the cooperation of cytoskeletal polymers and motors to generate the necessary forces for the division process. The dynamic reorganization of the cytoskeleton, cell organelles, and membrane molecules will lead to changes in cell elasticity.[4-7] This is an important biophysical property of the cell since it can be used to differentiate cancerous from normal cells[8] and can reflect changes in the chemical environment[9,10] or in response to genetic mutations.[11]

The cell cycle is separated into the interphase and mitotic phases. Interphase includes DNA synthesis and gap phases while the mitotic phase leads up to cell division,[12] which plays a vital role in cell proliferation and differentiation. The mitotic phase is managed by a complex and coordinated sequence of the membrane, cell organelle, and

cytoskeleton alterations that give rise to major morphological changes.[3,13] It can be simply divided into prophase, prometaphase, metaphase, anaphase, and telophase, and cytokinesis at the end of the division. At the beginning of cell division, microtubules release tubulins, and these tubulins assemble to form spindles to arrange chromosomes. In prometaphase, the nuclear membrane breaks apart and kinetochore microtubules emerging from the centrosomes at the poles of the spindle attach to the chromosomes. In metaphase, the condensed chromosomes line up in the middle of the cell. In anaphase and telophase, the cleavage furrow appears, and the chromosomes begin to separate. In telophase, the spindles gradually disintegrate, and the chromosomes reach their respective poles. These dynamic changes provide a cell with enough force to divide the mother cell into daughters at the end of the division. In the normal division process, the cell will undergo two-polar cell division since the centrosomes cluster into two poles, and in the abnormal division, the cell will undergo multipolar division since the extra centrosomes cluster into extra poles.

Atomic force microscopy (AFM),[14] an instrument for the study of surface properties, has been widely used to visualize, probe, and manipulate biological systems ranging from living cells to single molecule.[15-17] The possibility of measuring cell elasticity during division by using nanoindentation technique-based AFM was demonstrated. By using a discontinuous manner at identified phases, changes in the elasticity of cells during division have been observed. These changes are attributed to the variations in the lipid composition of the plasma membrane or moesin.[4,5] It also showed that furrow stiffening during cell division can be due to the accumulation of acto-myosin.[6] These studies were carried out on adherent cells, which require rounding up before the mother cell can divide, and the rounding force causes changes in the biophysical characteristics of the cell.[18] Although the change in elasticity at the furrow of the adherent cells during normal division has been investigated, the elasticity of the non-adherent cells, which do not require rounding up before division, during both normal and abnormal divisions remains unclear.

In this study, the nanoindentation-based AFM technique was used to continuously measure the elasticity of individual Jurkat T-cells in both synthesis and mitotic phases. This cell line is an immortalized line of human T lymphocytes that causes acute lymphoid leukemia, a disease that is characterized by the dysfunction of normal immune surveillance function in the body.[19,20] The results showed that the cell elasticity does not change during DNA synthesis phase while it significantly changes during division and gradually returns to the elasticity of the mother cell at the end of cytokinesis.

2 | METHODS

2.1 | Cell preparation

Jurkat cells, clone E6-1, (ATCC, TIB-152) were cultured in suspension in RPMI-1640 medium supplemented with 1% penicillin/streptomycin, 1% L-glutamine, and 10% heat-inactivated fetal calf serum (Invitrogen, Darmstadt Germany) at 37°C under a 5% CO_2 humidified atmosphere. An aliquot of the cell suspension was dropped onto a glass coverslip pre-coated with poly-L-lysine (PLL), which was already mounted onto the AFM biocell, for AFM measurements. The PLL coating glass was done as follows: 24-mm round glass coverslips (Plano GmbH, Wetzlar, Germany) were sonicated in turn in acetone, ethanol, and ultrapure water for 5 min followed by immersing into PLL solution 0.02% (Sigma Aldrich, Darmstadt, Germany) for 30 min. The coated substrates were dried with a N_2 blow.

2.2 | AFM measurements and data analysis

A Nano Wizard 3 AFM (JPK Instruments AG, Berlin, Germany) with a JPK Biocell combined with an inverted optical microscope model Olympus IX 81 (20x/0.45) was used. Tipless silicon nitride cantilevers (model MLCT-O10, Bruker AFM Probes, Camarillo, CA) with a nominal spring constant of 10 pN/nm were used. Silica microbead was attached to the end of the cantilever with glue NOA68 (Norland Products) under short wavelength UV light (254 nm) for 15 min before being exposed to oxygen plasma (600 W, oxygen flow 500 sccm, Gigabatch 310, PVA TePla, Wittenberg, Germany) for 1 min. The diameter of the beads of 4.3 ± 0.1 μm was determined by Zeiss Supra 40 VP scanning electron microscope (SEM) (Carl Zeiss AG, Jena, Germany). The spring constant of the cantilever with the attached bead of 12 ± 1 pN/nm was calibrated using the thermal noise method right before each measurement.

The cell height was estimated by the difference in the positions of the tip on top of the cell and on the substrate. The force-distance curves were measured in the force spectroscopy mode in a cell culture medium at 37°C with a speed of two force curves per second, an applied force of 200 pN, and a traveling distance (approach or retraction distance) of 2 μm. To measure the elasticity of nondividing cells, 64 to 100 force curves were recorded on an area of 2 × 2 μm^2 on top of a cell and the average elasticity of 100 cells was estimated. To track elasticity changes directly and continuously, the force curves were repeatedly measured on top of the cell in interphase and were measured at the location close to the cleavage furrow during division. To calculate elasticity, the approach curve of force curves were first converted into force-indentation curves and then fitted with Hertz model[21,22]:

$$F = \frac{4E\sqrt{R}}{3(1-\nu^2)}\delta^{3/2}, \quad (1)$$

where ν is Poisson's ratio ($\nu = 0.5$ for a soft sample), R is the radius of the bead, δ is the indentation depth, and E is cell elasticity. These were done with JPK data processing software version 4.4.18+. Origin software (version 9.1) was used for data analysis. The mean elasticity values and their corresponding SE of the mean were determined by applying Gaussian fits to the data. The statistic was determined using a one-way ANOVA test integrated in the origin software.

3 | RESULTS

3.1 | Elasticity of nondividing cell

Before investigating the mechanical characteristics of the cell during division, the elasticity of nondividing was examined by using nanoindentation-based AFM (Figure 1). Figure 1A shows a schematic model of nanoindentation measurement on a non-adherent cell adhered to PLL-coated glass surface. The AFM probe is positioned on top of the cell. Applying a force F to the cantilever, the cell will be indented and the force vs displacement (FD) curves will be measured. The approach force curves are then converted to force-indentation curves followed by fitting the resulting curves with the Hertz model to estimate the elasticity of the cell. Figure 1B shows an overlay of the optical and fluorescence images, which shows the silhouette of an AFM cantilever end placed on top of a cell (nuclear region, blue) for force measurements. Figure 1C shows the SEM image of the silica bead attached to the end of the AFM tip,

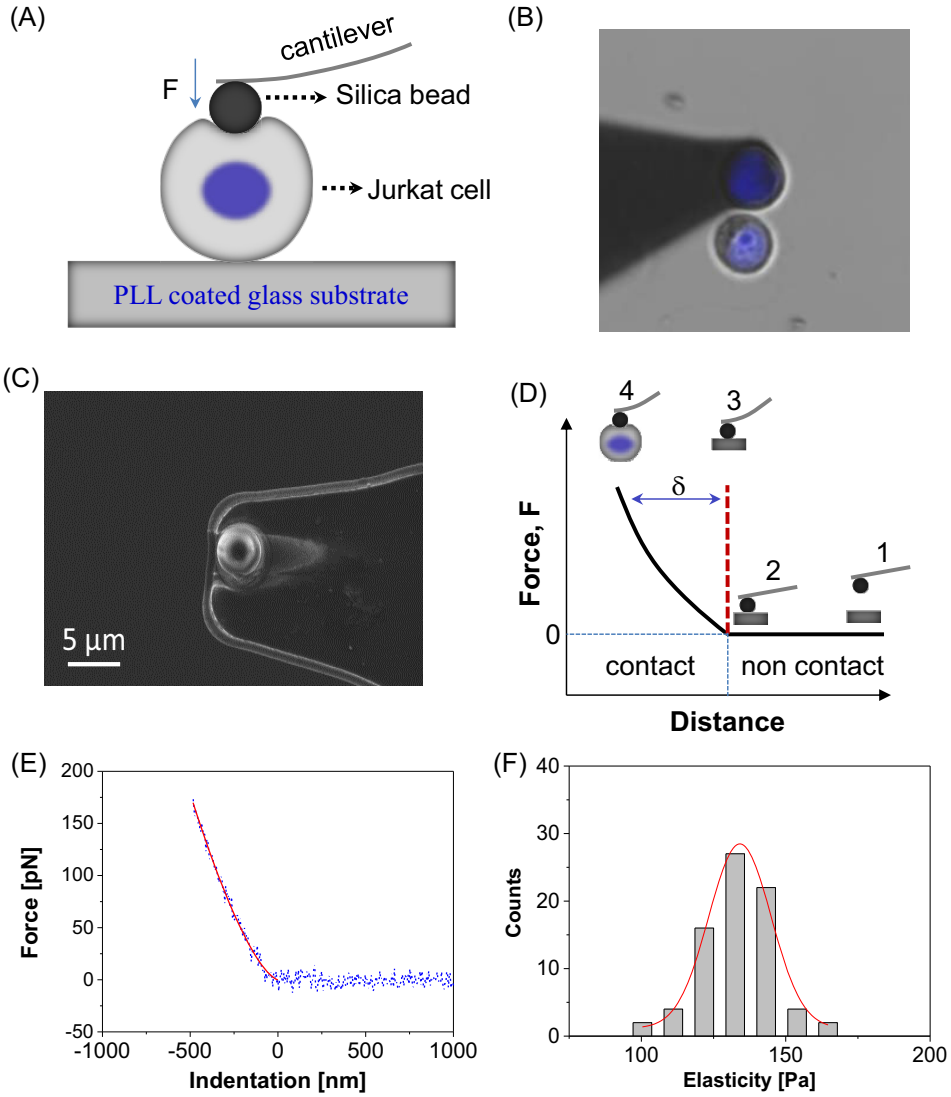

FIGURE 1 Cell elasticity measured by a spherical tip. (A) Scheme showing the force measurement on a nondividing cell adhered to PLL-coated glass substrate. (B) Overlay of the optical and fluorescence images showing the silhouette of the cantilever positioned on top of a cell. Blue areas are cell nuclei stained by DRAQ5. (C) Scanning electron microscopy image showing the spherical bead attached to the end of the AFM tip. (D) Schematic model showing an approaching force vs distance curve recorded on glass (dashed line) and cell (solid line) surface by AFM. When the sample surface is far away from the tip, the cantilever is not bent (1) and the force is equal to zero. Approaching the sample surface until it touches the tip (2), the cantilever starts to bend, and the force starts to increase. If the substrate is a hard glass surface, the cantilever (3) will proportionally bend with the extension of the AFM piezo stage, while if the substrate is a soft cell surface, the cantilever will bend (4) following an inward course. The force curve difference recorded on these two surfaces is the indentation depth (δ) of the cell. (E) Typical force-indentation curve converted from force-distance curve measured on top of the Jurkat T-cells (dashed line). The curve was fitted by the Hertz model (solid line) to calculate cell elasticity. (F) Elasticity histogram providing the mean elasticity value of the cell, which is obtained by Gaussian fitting (solid line).

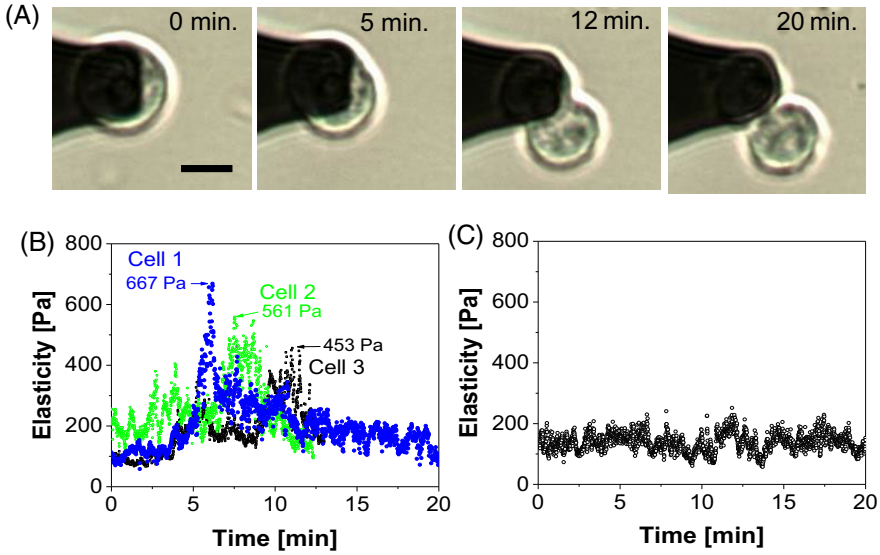

FIGURE 2 Real-time monitoring of elasticity of individual cells. (A) Optical images show a mother cell dividing into two daughters. The black trapezium at the left side of the images is the silhouette of the AFM cantilever. Scale bar: 10 μm. (B) Typical patterns show changes in cell elasticity during the division of three different cells. (C) Elasticity pattern of a non-dividing cell.

which was used for whole nanoindentation experiments in this study. Approaching the cell with a loading force F to the bead, the cell will be indented upon contact and the cantilever will be bent following an inward course of the indentation. The AFM will record this bending of the cantilever as input parameters of the F-D curve, which is schematically outlined as a solid curve (Figure 1D). The difference between force curves measured on soft cells (Figure 1D, black) and hard glass (Figure 1D, red) corresponds to the indentation depth, that is, how much the bead indents the cell. It is proved that the complication of the underlying hard substrate should be taken into account if the indentation depth exceeds 10% of the cell height.[23] Therefore, the cell height was first measured by approaching the glass surface and cell top to the bead before recording the cantilever positions on these two surfaces (total of five cells ranging from smaller to larger cells). The measured difference positions of the cantilever on the glass surface and on top of the cell are 10 to 15 μm, which is approximately equal to the cell height.

After estimating the cell height, F-D curves were measured and converted into force-indentation curves. Figure 1E shows a typical force vs indentation curve (dashed line) measured on a nondividing cell. The ~500-nm indentation depth curve indicates that the tip penetrated less than 10% of the cell height.The elasticity of the cell was estimated by fitting the curve with the Hertz model (red line) for a soft sample using a spherical tip. Figure 1F shows the elasticity histogram with a mean value ± SE of 134.5 ± 2.8 Pa.

3.2 | Cellular elasticity during normal division

During division, a massive rearrangement of the cell organelles causes changes in its biophysical characteristics. Especially the elasticity at the furrow of the adherent cell will be significantly changed due to the accumulation of actin and myosin.[6] To verify whether this characteristic will also change for non-adherent cells, the elasticity of the dividing Jurkat T-cells was investigated. In this work, the colloid probe was positioned on top of the mother cell and the force curves were continuously measured. During cell division, the colloid probe was kept close to the cleavage furrow. Figure 2A shows optical images of a normal dividing cell under the tip load. A low loading force was applied to minimize external interference to the cell condition. With a low force applied to measure cell elasticity, the proliferation and development of the cell were not significantly interfered as evidenced by the fact that the cell could still divide under the tip load. Figure 2B shows the elasticity profiles of three typical dividing cells.

Even though the absolute elasticity varies from cell to cell, a similar pattern of increasing elasticity at a certain time point can be seen for all cells. It clearly shows that when the cell entered mitosis, the elasticity of the mother cell significantly increased and that of the daughter cells gradually reduced to the elasticity value of the mother cell at the end of the division process. This change was not observed in the nondividing cell (Figure 2C). The elasticity of the cell during division could increase up to ~6-fold, and the time course of a normal cell division was from 3 to 20 min. The changes in the elasticity of the cells when they entered mitosis were different from cell to cell. However, they all ($n = 9$) showed a stiffening during division and gradually returned to the value of the mother cell at the end of cytokinesis. Statistical analysis showed that the elasticity of the cell during division is significantly different from that of either mother or daughter cells with $P < .05$. Several sudden and large alterations (peaks) of >3-fold of original elasticity during division are attributed to the irregular rearrangement of the actin filaments and cell organelles in combination with intermittent contraction of the contractile ring to separate mother cell into daughters, which creates tension over the cell. Additionally, other factors such as oscillation of the molecular motors or redistribution of the membrane molecules, etc. also cause changes in cell elasticity during division.

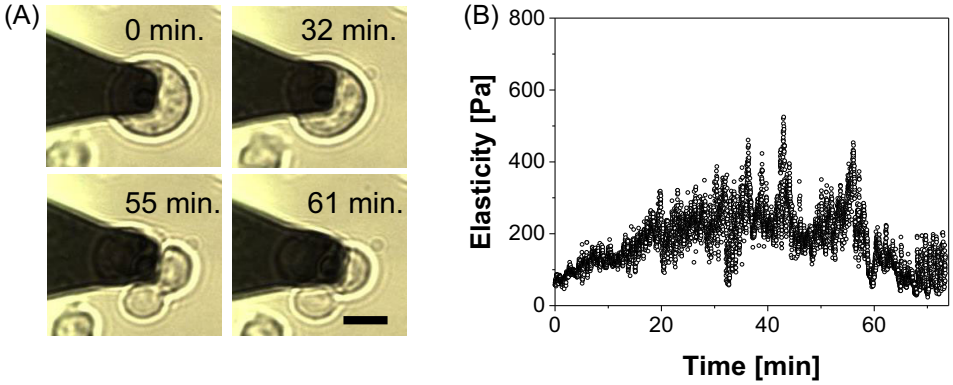

FIGURE 3 Time course of changes in elasticity of a cell during aberrant division. (A) Optical images show a mother cell dividing into three daughters. Scale bar: 10 μm. (B) Elasticity profile of the cell during abnormal division showing a change in cell elasticity following time.

3.3 | Cell elasticity during abnormal division

In some cases, a mother cell can divide into more than two daughters. It has been proved that extra-centrosome mediates multipolar spindle assembly and the cell undergoes multipolar anaphase that produces three or more mononucleated daughter cells.[24,25] Figure 3A shows optical images of a mother cell dividing into three daughters. In this abnormal division, the time required for the cell to complete the division process was ~1 h. The cell elasticity also increased after the cell entered mitosis and gradually returned to the value of the mother cell at the end of the division (Figure 3B). The mean elasticity of daughter and mother cells changed very much during the division.

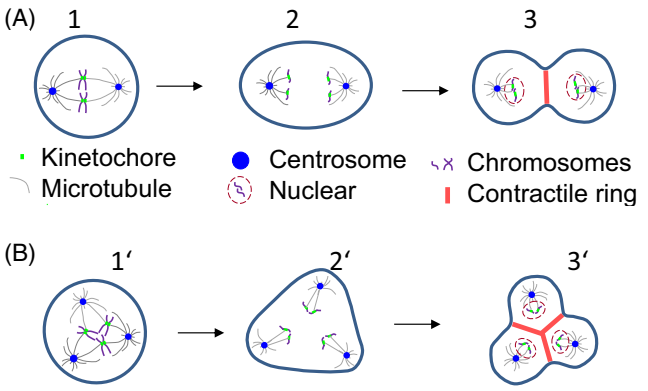

FIGURE 4 Scheme showing the reorganization of the cell organelles during division that caused oscillation of the cell elasticity. (A) In normal cell division process, kinetochore microtubules attach to the chromosomes, which align at the center of the cell at metaphase (1), separate them into sister chromatids, and pull them to the poles at anaphase (2). The contractile ring formed at the cell equator at telophase (3) will constrict to separate the mother cell into two daughters. (B) In the abnormal division process, chromosomes align in three or more directions at the cell center at metaphase (1′) and microtubules will drag them to the poles at anaphase (2′). At telophase (3′), the newly formed contractile ring will constrict to sever the mother cell into daughters.

4 | DISCUSSION

In this article, the elasticity of Jurkat T-cells was measured using a constant loading force. The resulting force-distance curves were converted to force-indentation curves and were fitted with the Hertz model. Dimitriadis and co-workers[26] showed, when estimating cell elasticity by the Hertz model, that the complication of the underlying hard substrate should be considered. This effect is less prominent for the pyramidal tip if local strains created by this tip do not exceed the linear-elastic assumption. However, this type of tip will provide a cell elasticity value of 60% higher than that measured by a spherical tip.[26] Applying this modified Hertz model to estimate cell elasticity showed that when indenting cells with a cell diameter of 12 μm by a bead of 4.3 μm, the apparent cell elasticity is overestimated by less than 1% for a modulus of 134 Pa. Thus, the underlying hard substrate did not significantly create complications to the result of the cell elasticity in this study. Even though the Hertz model fits well with the data, there are still errors in the absolute elasticity value when using this model for the calculation. This means that this model is applied to isotropic and homogeneous materials while Jurkat cells are inhomogeneous since they have a membrane, nucleus, cytoskeleton, and organelles. Regardless of the errors, this remains the main model to calculate the cell elasticity. The elasticity of nondividing Jurkat cells in this study is ~3-fold greater than that reported before.[27] Perhaps, this is the effect of cell immobilization on a hard surface as it often results in higher value than the non-immobilized cells. This result is also ~25-fold softer than that of the previous study.[28] This may be due to the effect of the tip geometry, experimental conditions, and other issues related to the AFM technique.[29]

Cell elasticity is an integrative parameter reflecting cell mechanics and is oscillating in standard physiological conditions. The oscillation is self-induced (spontaneous)[24,25] and the magnitude is different depending on cell state, cell type, or surrounding microenvironment. The cell elasticity oscillation can also be measured by applying a repetitive indentation technique. This approach allows not only time-resolving sequences of cell elasticity but also quantifying the magnitude of the oscillations.[30] In this study, this approach was applied to investigate the elasticity of both nondividing (interphase) and dividing cells. In interphase, the cell elasticity oscillates slightly, and this oscillation is generally powered by collectively working within assemblies of the molecular motors, which are related to various functions, such as contraction or movement of cell organelles.[31]

In the normal division process, supernumerary centrosomes commonly cluster into two poles, and therefore, cells will undergo two-polar cell division.[5] The cell elasticity during normal division does not significantly change when a cell undergoes from prophase to metaphase. This may be because the rearrangements of the cell organelles such as DNA chromosomes condensation, breakage of the nuclear envelope, attachments of sister chromatids to spindle microtubules through kinetochore, or alignment of the chromosome at the cell equator do not require much force, and therefore, cell surface is not so tensile. The increase in cell elasticity during normal division from metaphase to telophase may have a close correlation with the rearrangement of the cell organelles outlined in Figure 4A. As it undergoes from metaphase (1) to anaphase (2) to telophase (3), the microtubules pull strongly to separate sister chromatids to form two daughter chromosomes and the contractile ring constricts strongly to separate the mother cell into two daughters. These processes require strong forces that create tension over the whole cell surface, leading to a strong increase in cell elasticity. Moreover, the contractile ring is mainly composed of actomyosin, which is also an important factor that contributes to the increase in cell elasticity. At the end of mitosis, it also requires force to separate the cell into daughters but smaller than in metaphase, anaphase, and telophase and greater than events before metaphase. Therefore, there will be a slightly higher elasticity than events from prophase to metaphase. The change in cell elasticity of normal cell division observed in this study is consistent with traction patterns observed in dividing 3T3, Dictyostelium discoideum, HS1, or PTEN cells,[32,33] suggesting that the forces are important factors that contribute to the changes in cell elasticity.

The elasticity pattern is also similar to that reported for other adherent NRK fibroblast, PtK1, and PtK2 cells[6] except that at the end of the division in the current observation, the elasticity of the daughter cell tended to return to the values of the mother cells (Figure 2B). This may reflect different characteristics between adherent and non-adherent cell lines. Even though we did not investigate, it will be very interesting to compare with mother cells the elasticity changes of the daughter cells during division. We speculate that with the same applied force, a longer time is required for daughter cells to divide as compared with mother cells.

The chromosome of the mother cell during aberrant division is known to abnormally segregate.[34] This is due to the incorrect and uneven segregation of chromosomes that correlates with the presence of extra centrosomes. These extra centrosomes generate chromosomal instability by promoting multipolar anaphase, a highly abnormal division that produces three or more aneuploid daughter cells. The chromosomal instability is a major source of aneuploidy and tumor initiation and proliferation. The chromosomal instability is a major source of aneuploidy and tumor initiation and proliferation.[33-36] In most cases, a mother cell will undergo two-polar cell divisions and only a minor fraction of cells will undergo multipolar cell division. This means that in an abnormal division process, the chromosome of the mother cell will incorrectly segregate as schematically outlined in Figure 4B. It will segregate into three directions instead of lining up at the center of the mother cell at metaphase (1′) like in the case of normal cell division, and at anaphase (2′), the mother chromosomes will be separated into three sets of sister chromatids. After that, the contractile ring formed at telophase (3′) will continuously constrict to separate the mother cell into three daughters. In this abnormal division process, daughter cells will not inherit the complete set of chromosomes of the mother cell. This may explain the reason why daughter cells often die after division or before the second round of mitosis.[5] The change in cell elasticity, in this case, is also different from that of normal cell division. This may be because the cell may require more force to rearrange the cell organelles before the spindles pull the sister chromatids to the poles. This force creates tension over the cell surface, leading to an increase in cell elasticity right after the cell enters mitosis. Further studies may be necessary for a precise conclusion for this phenomenon.

In summary, the approach of repetitively measuring the elasticity as a model for non-adherent Jurkat T-cell allows real-time monitoring of the changes in cell elasticity during division with high time resolution. Together with the accumulation of the actomyosin at the furrow to form a contractile ring, the force required to rearrange cytoplasmic and surface molecules and to pinch the contractile ring to separate mother cell into daughters are also important factors that contribute to the change in cell elasticity. Thus, a direct, high time resolution measurement of the cell elasticity can provide insight into involved molecules and the mechanism of cell division processes.

AUTHOR CONTRIBUTIONS

Van-Chien Bui designed the research study, performed the experiments, analyzed the data, and wrote the manuscript, Thi-Huong Nguyen discussed the data and wrote the manuscript. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no competing interests.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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