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Letter

Mechanically Regulated Biphasic Chromatin Dynamics during Cellular Necrosis

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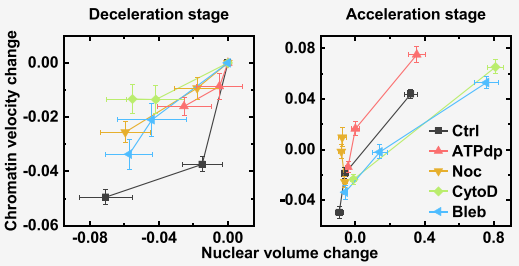
ABSTRACT: Necrosis, long considered an uncontrolled and passive process, is now known to involve active cellular regulation. While significant research has focused on biochemical pathways of necrosis, the physical changes within the nucleus, particularly chromatin dynamics, remain unknown. By combining the single-particle tracking of telomeres and particle image velocimetry of global chromatin, we characterize the spatiotemporal evolution of chromatin dynamics during necrosis. We reveal a distinct biphasic pattern of chromatin motion with an initial deceleration followed by a late acceleration, accompanied by a transient increase and a subsequent decrease in intranuclear spatial heterogeneity. Through systematic perturbation, we establish a stage-specific regulatory model: the early deceleration of chromatin is driven by mechanical restraint from the cytoskeletal network, while the late acceleration results from the combined effects of nuclear swelling and DNA fragmentation. Our findings highlight necrosis as a programmed process, uncovering a previously unrecognized layer of cytoskeleton-mediated mechanical regulation in cell death.



Cell death is a fundamental biological process essential for tissue homeostasis and organogenesis.[1−3] Necrosis, a form of cell death characterized by cellular swelling and early plasma membrane rupture,[4,5] has historically been viewed as an uncontrolled, catastrophic event resulting from severe external stress. However, growing evidence recently shows that necrosis can be a tightly regulated, programmed process, sparking intense interest in its underlying mechanisms.[6−8] While much research has focused on the biochemical pathways governing regulated necrosis, the corresponding biophysical changes, particularly within the nucleus, remain largely unexplored. As the nucleus houses the cell's genome in the form of chromatin, understanding the evolution of chromatin dynamics is a critical next step in deciphering the regulation of necrosis.

Investigating intranuclear dynamics during necrosis is crucial because the nucleus possesses a unique physical environment, distinct from the cytoplasm, which is primarily defined by the hierarchical organization of chromatin.[9−11] The spatial arrangement and movement of chromatin are not merely passive but are actively modulated.[12−17] For example, mechanical forces generated by the cytoskeleton can be transmitted directly to chromatin through the LINC complex.[12,13] Since necrosis involves dramatic cytoskeletal and cytoplasmic reorganization such as microfilament remodeling,[18] mitochondrion dilatation,[4] and an increase as well as a transition from anisotropy to nearly isotropy in cytoplasmic diffusion,[19] it is critical to ask how these events are propagated to the nucleus and how they impact chromatin behavior. Characterizing these dynamics will therefore provide novel biophysical insights into the nuclear response during cell death, complementing the current biochemical models and potentially revealing new aspects of necrotic regulation.

Here, we investigate the spatiotemporal characteristics of chromatin dynamics during necrosis as well as the underlying regulation mechanisms by combining single-particle tracking (SPT) of telomeres and particle image velocimetry (PIV) analysis of global chromatin. Strikingly, we observe that chromatin motion exhibits a nonmonotonic evolution, with an early deceleration stage and a subsequent acceleration stage. Additionally, the heterogeneity in chromatin motion between the central and the perinuclear regions first enhances and then diminishes. By systematically exploring the effect of ATP, cytoskeletons, and nuclear volume on the evolution of chromatin dynamics, we find that the early deceleration is directly regulated by cytoskeletons, while the late acceleration is attributed to nuclear swelling and chromatin fragmentation. Our results augment current understanding of necrosis, providing vital clues to the biophysical regulation of dying cells.

To induce necrosis, we treat HEK293T cells with 20 mM H_2O_2[20] and confirm the characteristic progression of cell blebbing, swelling, and eventual plasma membrane rupture via propidium iodide (PI) staining[5] (Figure 1A and Figure S1). We first track the dynamics of individual telomeres, labeled

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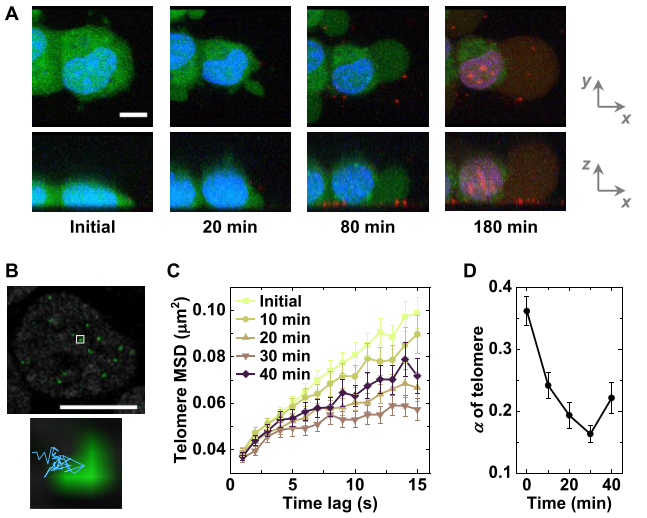

Figure 1. Necrosis and telomere dynamics. (A) Snapshots of cells undergoing necrosis from top (upper row) and side (lower row) view. Cells are stained with CellTracker (green), Hoechst 33342 (blue) and PI (red). (B) Telomeres labeled with TRF1-eGFP. The lower panel shows an enlarged telomere focus (marked by a white square in the upper panel) and the trajectory of it over 40 s. (C) MSD of telomere focus during necrosis. (D) Diffusion exponent α of the telomere over time during necrosis. Scale bars, 10 μm. Statistics for telomeres in 18 cells are presented as mean ± SE.

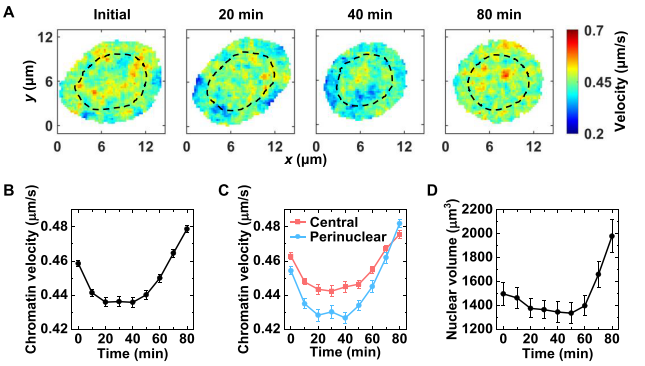

Figure 2. Chromatin dynamics and nuclear volume during necrosis. (A) Velocity magnitude maps of chromatin in a nucleus. The dashed line separates the nucleus into the central region and the perinuclear region, with each region approximately occupying 50% of the nuclear area. (B) Average chromatin velocity magnitude in a nucleus over time. (C) Average chromatin velocity magnitude in the central and perinuclear regions of a nucleus over time. (D) Nuclear volume over time. All statistics above are presented as mean ± SE with n = 20 cells.

with telomeric repeat binding factor 1 tagged with enhanced green fluorescence protein (TRF1-eGFP),[21] using SPT[22−24] (Figure 1B). Strikingly, the mean squared displacement (MSD) of telomeres reveals a nonmonotonic trend, first decreasing and then increasing as necrosis progresses (Figure 1C). The diffusion exponent α, an indicator of the mode of motion, mirrors this pattern, showing an initial decrease followed by an increase (Figure 1D).

To determine if this behavior is representative of the entire nucleus, we map global chromatin flow through labeling global DNA with Hoechst 33342, videoing cells at a 1-s interval, and employing PIV algorithm,[14,25] to calculate the velocity vector field of chromatin diffusion within the nucleus, with the overall drift of the nucleus being subtracted (Figure S2).[16] Since the velocity direction exhibits a stochastic and uniform distribution (Figure S3), we focus on the velocity magnitude field (Figure 2A) in the subsequent analyses. The average velocity magnitude of chromatin diffusion across the nucleus also displays a biphasic pattern of early deceleration followed by late acceleration, consistent with the telomere tracking data (Figure 2A,B). Collectively, these results establish that chromatin motion follows a distinct two-stage evolution during necrosis.

We notice that the chromatin velocity exhibits spatial heterogeneity from PIV maps (Figure 2A), which is consistent with the known spatial organization of the nucleus—with euchromatin concentrated centrally and heterochromatin enriched at the periphery.[26] We next investigated the spatial characteristics of chromatin motion by partitioning the nucleus into central and perinuclear regions (Figure 2A). Before necrosis, chromatin in the central region moves faster than in the perinuclear region, consistent with a more open chromatin state. Upon the induction of necrosis, chromatin motion slows in both regions, but the deceleration is more pronounced at the periphery (Figure 2A,C). This enhances the velocity difference between the two regions, suggesting an increase in structural heterogeneity. As necrosis progresses into the acceleration stage, the velocity increases in both regions but more rapidly at the periphery, thereby diminishing the initial velocity difference (Figure 2A,C). This nonmonotonic evolution of spatial heterogeneity points to a programmed regulation of nuclear architecture during necrosis.

Next, we seek to investigate the regulators of the evolution of chromatin dynamics during necrosis. Since intranuclear dynamics is influenced by crowding,[27,28] we measure nuclear volume throughout the necrotic process. The nucleus first undergoes shrinkage (pyknosis) before swelling in the later stage (Figure 2D), consistent with previous studies.[29] However, the timing of these volume changes is decoupled from the observed chromatin dynamics. For instance, chromatin velocity stabilizes between 20 and 40 min while the nucleus continues to shrink, and the acceleration of chromatin motion at 50 min precedes the onset of nuclear swelling at 60 min. This temporal decoupling strongly suggests that the evolution of chromatin dynamics is not a passive consequence of changes in nuclear crowding but is instead governed by active regulatory mechanisms.

To dissect these regulatory mechanisms, we first deplete intracellular ATP by treating cells with 50 mM 2-deoxy-D-glucose (2-DG) and 10 mM NaN_3 prior to necrosis induction.[30] Cytotoxicity examinations have confirmed that these drugs are noncytotoxic at the working concentrations used throughout the experiment period (Figure S4). In ATP-depleted cells, chromatin velocity also decreases first and increases subsequently during necrosis, but the deceleration extent as well as the deceleration rate is smaller compared to the control cells (Figure 3A and Figure S5A). The velocity disparity between the central and perinuclear regions disappears (Figure 3B and Figure S5A), implying that ATP plays a vital role in maintaining nuclear architecture and corresponding functions. Moreover, the nuclear volume decrease is hindered to a certain extent (Figure 3C), verifying that nuclear pyknosis is an active, ATP-dependent process.[29]

We next investigate the role of the cytoskeleton.[13−15] To do so, we employ specific pharmacological inhibitors to perturb cytoskeletal components. Cytotoxicity examinations have

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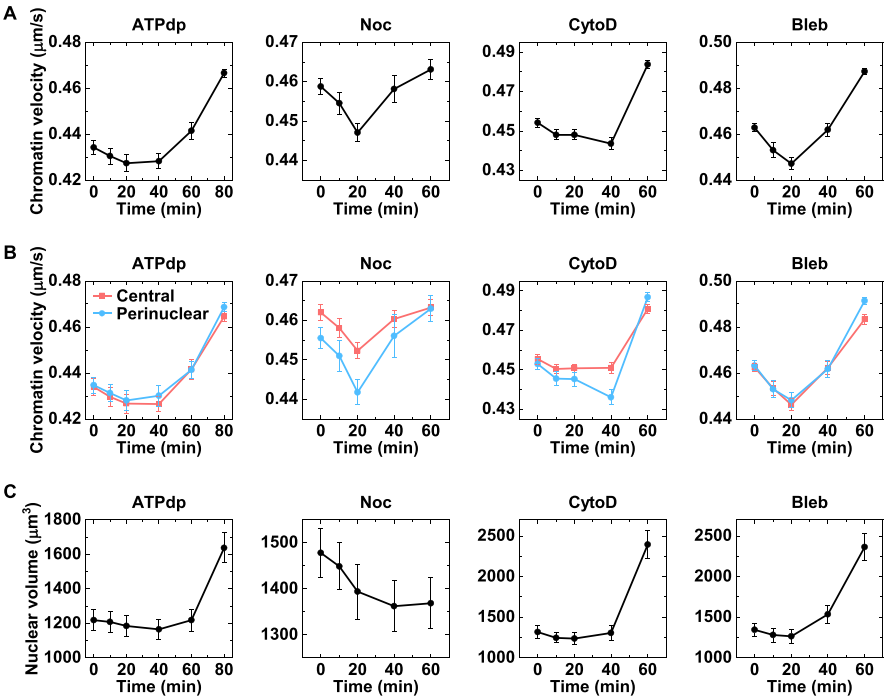

Figure 3. Chromatin dynamics and nuclear volume in necrotic cells subjected to ATP depletion (ATPdp), microtubule disruption (Noc), microfilament disruption (CytoD), or myosin II inhibition (Bleb). (A) Average chromatin velocity magnitude in a nucleus over time. (B) Average chromatin velocity magnitude in the central and perinuclear regions of a nucleus over time. (C) Nuclear volume over time. All statistics above are presented as mean ± SE with n = 20 cells.

verified that these inhibitors are noncytotoxic at the working concentrations used throughout the experiment period (Figure S4). Disruption of microtubules (with nocodazole[2]) or microfilaments (with cytochalasin D[22]), or inhibition of motor protein myosin II (with blebbistatin[2]) does not eliminate the biphasic pattern of chromatin dynamics during necrosis (Figure 3A and Figure S5B–D). Notably, inhibiting myosin II eliminates the baseline velocity difference between the central and the perinuclear regions (Figure 3B and Figure S5D). This directly implicates the crucial role of actomyosin contractility in maintaining the spatial organization of the nucleus. Further we examine how cytoskeletal perturbations affect nuclear volume. Microtubule disruption causes progressive nuclear shrinkage without subsequent swelling even as chromatin motion recovers (Figure 3C). This persistent volume decrease demonstrates that microtubules regulate nuclear volume independently of chromatin dynamics. In contrast, both microfilament disruption and myosin II inhibition produce exaggerated biphasic responses, with an initial mild shrinkage followed by dramatic swelling (Figure 3C). These distinct patterns reveal that actomyosin contractility coordinately regulates both nuclear architecture maintenance and volume control during necrosis. Together, these findings reveal distinct cytoskeletal regulation of chromatin dynamics and volume changes during necrosis.

A systematic comparison of all conditions confirms that ATP depletion and all cytoskeletal perturbations significantly reduce the magnitude and rate of the initial deceleration (Figure 4A). A parallel analysis of nuclear volume changes reveals distinct cytoskeletal contributions (Figure 4B): while microfilaments and myosin II generate compressive forces that promote pyknosis and limit swelling, microtubules provide opposing tensile forces that facilitate nuclear expansion. To dissect the underlying mechanisms of the chromatin dynamics evolution,

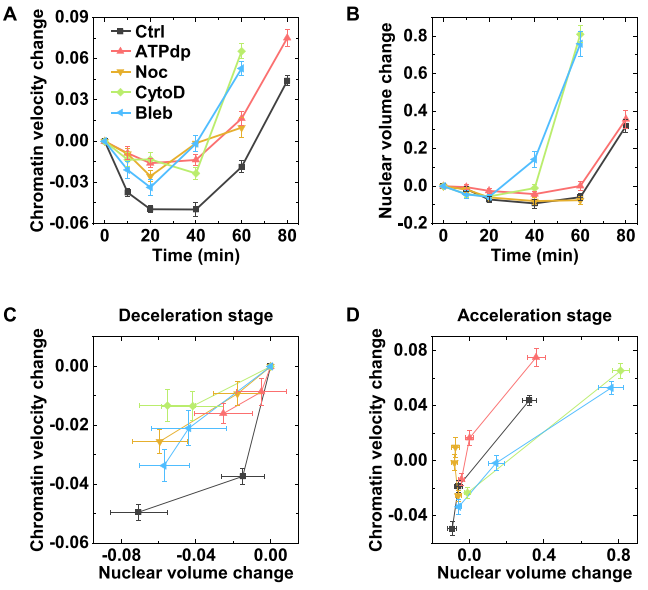

Figure 4. Systematic analysis on the change of chromatin velocity and nuclear volume in necrotic cells under control (Ctrl), ATP depletion (ATPdp), microtubule disruption (Noc), microfilament disruption (CytoD), and myosin II inhibition (Bleb). (A) Change of chromatin velocity magnitude over time. (B) Change of the nuclear volume over time. (C, D) Correlation between chromatin velocity magnitude change and nuclear volume change during the deceleration stage (C) and the acceleration stage (D). All statistics above are presented as mean ± SE with n = 20 cells.

we analyze the correlation between chromatin velocity and nuclear volume during deceleration and acceleration stages, respectively. During the deceleration stage, the chromatin deceleration is consistently attenuated by cytoskeletal

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perturbations (Figure 4C). This demonstrates that the cytoskeleton restricts chromatin mobility in early necrosis. In contrast, during the acceleration stage, chromatin velocity shows a positive correlation with nuclear swelling across most conditions (Figure 4D). However, in microtubule-disrupted cells, chromatin accelerates even without nuclear expansion, suggesting an additional driver. Given that necrosis is associated with DNA damage,[31] we attribute this acceleration to chromatin fragmentation.

Taken together, our findings support a stage-specific regulatory model: the early deceleration of chromatin is driven by mechanical restraint from the cytoskeletal network, while the late acceleration results from the combined effects of nuclear swelling and DNA fragmentation. Noted that in addition to cytoskeletons, the mechanical factors within the nucleus could affect chromatin dynamics during necrosis. For example, nuclear lamina is known to provide mechanical support for nuclear envelope and serve as anchoring sites for perinuclear chromatin.[11,26] And nucleoskeletons, like nuclear actin and myosins, also have an impact on intranuclear architecture and dynamics.[32] Future studies on the integrated mechanical network of nuclear lamina, nucleoskeletons, and cytoskeletons would facilitate our understanding of the mechanisms underlying the spatiotemporal evolution of chromatin dynamics during necrosis.

In this study, we provide the first characterization of the spatiotemporal evolution of chromatin dynamics during necrosis. We uncover a distinct biphasic pattern, wherein an initial cytoskeleton-mediated deceleration of chromatin is followed by a subsequent acceleration driven by nuclear swelling and DNA fragmentation. Spatially, this process is accompanied by a transient increase and then a decrease in the motional heterogeneity between the nuclear core and the periphery, indicating a programmed alteration of nuclear architecture.

A key finding of our work is the decoupling of chromatin dynamics from changes in the nuclear volume. This contrasts with observations in the cytoplasm during necrosis, where intracellular diffusion is largely dictated by cell swelling and crowding.[19] Our results challenge the classical view of necrosis as a passive event by identifying the cytoskeleton as a critical regulator of chromatin and nuclear response. By demonstrating that cytoskeletal networks directly mediate early chromatin deceleration through mechanical restraint, we reveal a previously unrecognized layer of mechanical control governing this form of cell death. Our work provides a foundation for exploring novel strategies to manipulate cell death in both physiological and pathological contexts.[1,8]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpclett.5c02729.

Detailed experimental methods, data analysis procedures, and supplementary figures showing nuclear volume changes, chromatin velocity analysis, and cytotoxicity assays (PDF)

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Notes

The authors declare no competing financial interest.

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