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Nuclear envelope rupture: little holes, big openings

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The nuclear envelope (NE), which is a critical barrier between the DNA and the cytosol, is capable of extensive dynamic membrane remodeling events in interphase. One of these events, interphase NE rupture and repair, can occur in both normal and disease states and results in the loss of nucleus compartmentalization. NE rupture is not lethal, but new research indicates that it could have broad impacts on genome stability and activate innate immune responses. These observations suggest a new model for how changes in NE structure could be pathogenic in cancer, laminopathies, and autoinflammatory syndromes, and redefine the functions of nucleus compartmentalization.

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Introduction

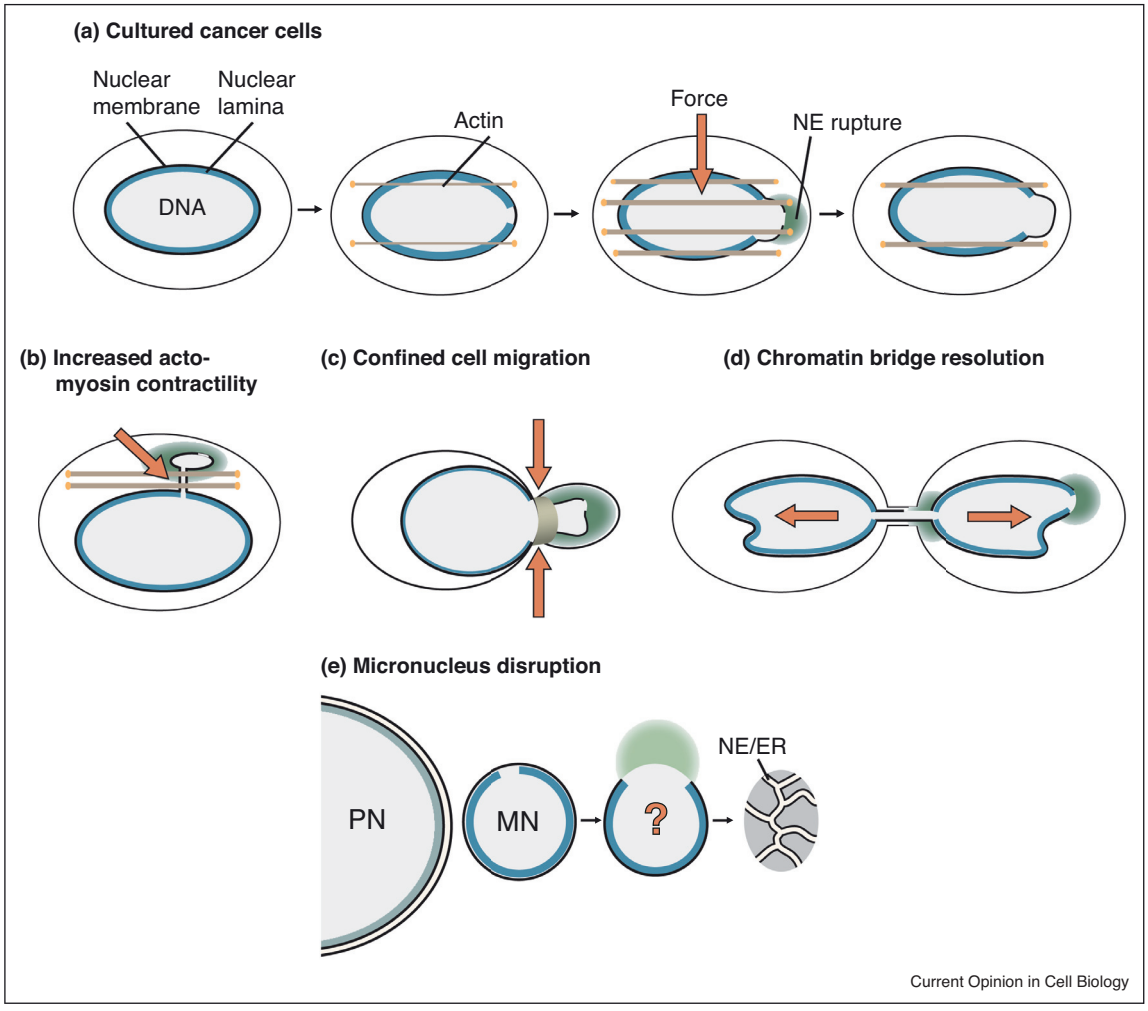
The nuclear envelope (NE) surrounds the nucleus and is comprised of two membrane sheets fused at the nuclear pore complexes enclosing a lumen that is contiguous with the endoplasmic reticulum. The other main components of the NE are the nuclear pore complexes (NPCs) and the underlying nuclear lamina, a meshwork of lamin intermediate filament and transmembrane proteins that connect the chromatin to the inner nuclear membrane. The structure and composition of the NE regulates many aspects of nucleus biology, including nucleus morphology, response to mechanical stress, heterochromatin binding, gene expression, and nuclear functions, such as DNA damage repair, which led to a model of the NE as a scaffold [1,2]. Recently, a new model of NE structure has emerged that highlights an essential requirement for interphase NE remodeling in many cell processes and behaviors [3]. Most of these dynamics preserve nucleus compartmentalization [2]. The exception is NE rupture, which results in the loss of nucleus compartmentalization and can be corrected by NE repair or lead to persistent chromatin mislocalization [4–7].

Analysis of the current examples of NE rupture indicates that this process can have both protective and pathogenic consequences, depending on the biological context. Transient NE rupture during cell migration is thought to release intranuclear pressure [8], which could facilitate nuclear deformation and migration through small pores. However, it is also correlated with increased genome instability and nucleus fragmentation [9••,10••,11]. Similarly, NE rupture in micronuclei can generate highly rearranged chromosomes [12], but may also stimulate senescence and clearance of aneuploid cells from tissues [13••,14•]. Finally, induction of pro-inflammatory responses after NE rupture may have a dual nature, triggering autoinflammatory disease in some contexts [15••], but also able to cause systemic anti-tumor responses after irradiation [13••,16•]. These observations raise new questions about the function of nucleus compartmentalization and the importance of regulating NE remodeling to prevent disease.

Interphase NE rupture and repair

Interphase NE rupture is defined as the loss of nucleus integrity due to membrane rupture in interphase and is characterized by rapid mislocalization of nuclear and cytoplasmic proteins in the absence of chromatin condensation [4–6]. Ruptures in the nuclear membranes typically occur at a single spot, often at sites of chromatin herniation [4–6]. Transient NE rupture, where membrane repair occurs within a few minutes to a few hours, has been observed in several conditions [9••,10••,17–21] (Figure 1). NE rupture without repair occurs frequently in micronuclei [7], small nuclei that form in addition to the primary nucleus as a result of chromosome missegregation. Micronuclei are distinct from nuclear buds, which often resemble micronuclei in shape but are connected to the primary nucleus via a thin chromatin bridge [22]. Micronuclei arise from many causes, including unrepaired DNA damage, defects in spindle assembly, and chromatin bridge breakage [23]. Persistent NE rupture in micronuclei has been observed in cultured cells after missegregation of whole chromosomes or acentric fragments, due to spindle misassembly or DNA damage, and in tumor cells and embryos *in vivo* [7,13••,15••,24,25]. In cycling cells the chromatin from disrupted micronuclei is not lost, but persists in the cytosol and frequently reincorporates into the primary nucleus in the next cell cycle [7,26].

Figure 1



Mechanism of nuclear envelope rupture. **(a)** Nuclear envelope rupture in cultured cancer cells occurs as a result of defects in nuclear lamina organization that give rise to gaps in the lamina meshwork. Confinement by actin bundles increases stress on the nuclear membrane and results in chromatin herniation and rupture of the nuclear membranes. After rupture, the nuclear membrane is resealed. Nuclear lamina defects and increased membrane stress are also associated with NE rupture in laminopathy mutations (not pictured), **(b)** increased actomyosin contractility, **(c)** cell migration through narrow channels, and **(d)** chromatin bridge resolution. In contrast, NE rupture in **(e)** micronucleus disruption requires nuclear lamina defects, but the role of membrane stress is unknown.

Analysis of NE rupture has identified two significant contributors to NE stability — nuclear lamina organization and mechanical stress (Figure 1). Membrane rupture occurs at the site of gaps in the nuclear lamina, which can appear after mitosis or form during mechanical stress [4–7,9••,10••,18,19,20•]. In addition, membrane rupture can be inhibited by overexpressing lamin proteins [6,7,18], and occurs more frequently in cell types characterized by altered lamina structure [20•,27], indicating that nuclear lamina disorganization is required for NE rupture. NE rupture is frequently observed in nuclei experiencing significant mechanical stress [9••,10••,18,19,20•,27,28], and a current model is that external force on the nucleus triggers chromatin herniation and membrane rupture at sites of nuclear lamina breaks. One exception to this model is micronucleus disruption, where membrane rupture frequently occurs hours after the appearance of lamina gaps and does not depend on actin-based forces [7,19•]. The ESCRT-III membrane remodeling complex, which seals the NE after mitosis and in response to nuclear pore defects [29–31], is transiently recruited to sites of NE rupture and increases the efficiency of NE repair [9••,10••]. Nuclear lamina proteins are also recruited to the rupture site and persist after membrane resealing [10••,32]. Although significant progress has been made on the mechanism of NE rupture and repair, many questions remain about the molecular and mechanical