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Cell biology

Ripping up the nuclear envelope

Jennifer Lippincott-Schwartz

During cell division, the membranes that surround the nucleus must be dismantled to allow the DNA housed inside the nucleus to be partitioned into two daughter cells. New work shows how this happens.

One of the many events that take place as cells divide is the breakdown of the nuclear envelope — the membrane that surrounds the nucleus. Given the elaborate structural organization of the nuclear envelope[1], this is not a simple task. Rather unusually, the envelope consists of not one but two layers of membrane, which are punctuated by pores through which molecules can be moved into and out of the nucleus. Not only that, but branching off the surface of the outer layer is another membranous compartment, the endoplasmic reticulum. So how do cells dismantle the nuclear envelope?

Beaudouin and colleagues[2] and Salina and co-workers[3] have put forward a likely model in a recent issue of *Cell*. The authors provide evidence that a molecular motor protein, cytoplasmic dynein, is used to tear the envelope, transporting pieces of membrane away along filamentous structures called microtubules. The results reveal a new type of function for a molecular motor, and may provide insight into how other organelles are taken apart.

But why do dividing cells need to break down the nuclear envelope at all? The answer lies in the mechanics of nuclear division (mitosis). Before mitosis begins, the cell duplicates its chromosomes. During mitosis, the two chromosome copies ('sister chromatids') are partitioned to opposite poles of the cell, which then divides into two. To achieve such partitioning, the sister chromatids are first attached to the spindle — a structure composed of microtubules — that itself links to two microtubule-organizing centres, or 'centrosomes'. The microtubules then shrink back towards the centrosomes, pulling the sister chromatids apart. The problem is that, in many cells, the centrosomes are located outside the nucleus (that is, in the cytoplasm) during early stages of mitosis, whereas the sister chromatids are, of course, inside the nucleus. Unless the nuclear envelope breaks down, microtubules cannot attach to and partition the chromatids.

The mechanism by which the nuclear envelope breaks down has been the subject of much debate[4]. The traditional view is one involving vesiculation, in which, at the start of mitosis, nuclear-envelope membranes are converted into small vesicles that disperse into the cytoplasm. The idea has received support from subcellular 'fractionation' studies. But direct visualization of mitotic cells expressing fluorescent envelope proteins has shown that these proteins move freely throughout a single, continuous endoplasmic reticulum (ER) membrane system, with no evidence of vesicular intermediates[5,6]. These results have led to an alternative model that involves release and diffusion of envelope proteins and lipids into the ER, probably as a result of phosphorylation events, which abolish protein interactions essential for nuclear-envelope integrity.

But there is a problem with this model, which has to do with the need to quickly remove the nuclear envelope from the vicinity of chromosomes to allow the spindle apparatus to assemble and function. Diffusion into the ER takes time and does not immediately remove the membranes around the nucleus. Beaudouin *et al.*[2] and Salina *et al.*[3] provide a neat solution to the problem. Together they show that, after initiating nuclear-envelope breakdown by a force-driven tearing process, dynein quickly transports pieces of envelope, still attached to the ER, away from chromosomes along microtubules. At the same time, envelope lipids and proteins are mixed with ER components.

The first hint of a mechanistic link between microtubules and nuclear-envelope breakdown came nearly 40 years ago, when classic electron-microscopic studies showed an intimate connection between the spindle and nuclear envelope, as well as the presence of deep invaginations in the nuclear envelope near centrosomes[7]. It was first thought that these invaginations represent sites at which spindle microtubules 'pierce' the membrane[8]. But, when Beaudouin *et al.* looked at nuclear-envelope breakdown in living cells, they discovered something quite different (Fig. 1): invaginations result when spindle microtubules pull on nuclear membranes in the direction of centrosomes. More precisely, the authors found that microtubule-dependent forces mechanically stretch the nuclear lamina — the tight mesh

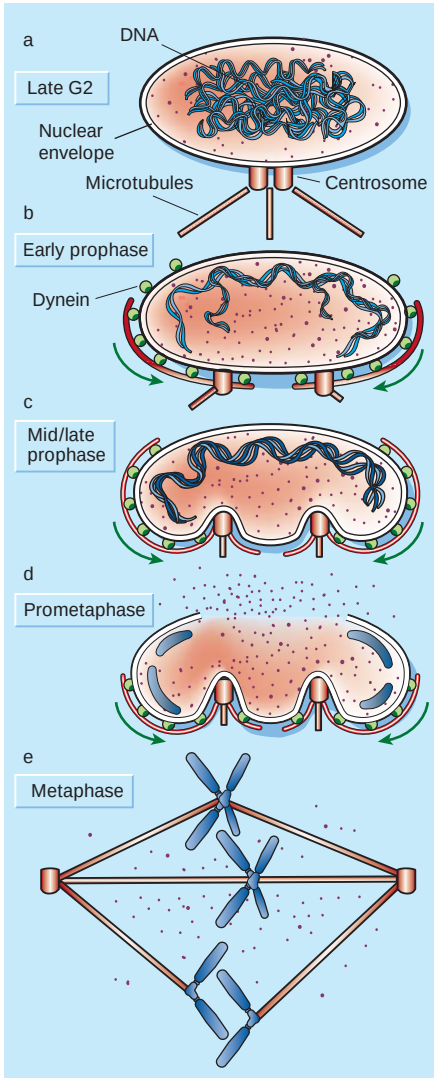

Figure 1 **How cells dismantle the nuclear envelope during the phases (shown in boxes) of cell division, as proposed by Beaudouin *et al.*[2] and Salina *et al.*[3].** a, **Chromosomes have been duplicated and are in an 'uncondensed' state. The centrosome has likewise been duplicated and is found just outside the nucleus.** b, **The molecular motor dynein is recruited to the nuclear envelope and interacts with microtubules.** c, **Dynein pulls nuclear-envelope components along the microtubules towards the centrosomes, causing invaginations.** d, **Withdrawal of membrane from the opposite side of the nucleus creates membrane tension, causing tearing. The nuclear envelope opens up catastrophically as the membranes continue to be pulled towards centrosomes. From early prophase onwards, the chromosomes are condensing into well-resolved forms and, after nuclear-envelope breakdown, can be attached to microtubules and segregated** (e).

of cytoskeletal proteins just inside the nucleus — and deform nuclear membranes, perturbing the distribution of nuclear-pore complexes and the ER.

Subsequent perforation of the nuclear envelope occurs not at the sites of invagination but on the opposite side of the nucleus, where tension is greatest. Once torn in this way the nuclear envelope catastrophically loses its shape, and cytoplasmic proteins flood into the nuclear space. It is not clear exactly how the initial perforation comes about. One clue comes from the finding that, in starfish embryos, the envelope becomes permeable to macromolecules (which are normally excluded from the nucleus by nuclear-pore complexes) before it is perforated[6]. So it is possible that microtubule-dependent changes in envelope structure might induce localized disassembly of nuclear pores, creating an epicentre for tearing.

The influx of cytoplasmic molecules that occurs after perforation might facilitate several mitotic processes, including chromosome condensation and spindle formation. Indeed, Beaudouin *et al.* show that chromosome condensation, which begins before nuclear-envelope breakdown, accelerates threefold after perforation. All in all, microtubule-dependent tearing seems to allow cells to tightly coordinate nuclear-envelope breakdown with spindle formation and chromosome dynamics.

Meanwhile Salina *et al.*[3] looked at the molecular basis of microtubule-dependent nuclear-envelope tearing, and find that cytoplasmic dynein becomes redistributed to the cytoplasmic face of the envelope before it invaginates. Once there, dynein associates with dynactin — an activator of dynein-mediated transport processes[9] — and pulls nuclear membranes and other envelope components along microtubules towards the centrosome.

It could prove challenging to work out exactly how dynein binds to the nuclear envelope. This protein is involved in many cellular processes and interacts with many structures and proteins. One possibility is that it associates with membranes through spectrin, a protein that — with dynactin — forms a lattice around organelles[10]. Whatever the case, dynein clearly transmits force across the nuclear envelope, as tearing disrupts both the inner and outer layers. This points to the possibility that dynein interacts with molecules associated with the nuclear-pore complexes, which span both layers. Another issue that needs to be resolved is how dynein is redistributed to the nuclear envelope from its usual cytoplasmic location in a cell-division-dependent way. Such redistribution might be controlled, at least in part, by the phosphorylation of dynein[11].

Might the mechanism described by Beaudouin *et al.*[2] and Salina *et al.*[3] be more generally applicable? The ER, mitochondria and Golgi apparatus all need to partition into daughter cells during mitosis, and a pulling and tearing mechanism dependent on dynein and microtubules could be at work here, too. In fact, the Golgi apparatus does split into two populations that follow centrosomes to different positions in the cell before being absorbed into the ER[12], and mitotic Golgi remnants have been shown to be swept towards centrosomes[13]. It remains to be seen whether or not dynein is involved. But its function in nuclear-envelope breakdown is now clear, and provides a good illustration of how two fundamental cellular processes — motor-driven transport and organelle breakdown — can be coordinated. ■

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Human evolution

Tangled genetic routes

Rebecca L. Cann

It is generally accepted that early human evolution took place in Africa, with human populations spreading from there. Using genetics to trace events in more detail remains a challenging task.

How best can the riches of human genetics be mined for information about our history and geography? In the tradition of human population genetics advanced over the past 50 years[1], the search is on for evidence of the isolation, adaptation and dispersal of populations over time. In this case, there is no digging for fossils, no three-dimensional reconstructions of skulls and such, just the requirement to collect 10-ml samples of blood. However, we are sometimes at a loss to disentangle population structure from population history. The diversity of DNA sequences in a modern population is an accumulation of events in the remote past. But it is unclear that the same forces that change allele frequencies (the incidence with which different gene forms occur) also change the genealogies of genes.

On page 45 of this issue[2], human phylogeographers — who study the geographical distribution of genealogical lineages using DNA sequence variation[3] — acquire a new approach to a recurrent problem. Alan Templeton[2] has analysed 11 different human gene trees with the program GEODIS[4]. His aim has been to assess the strength of the geographical signals they contain, using tests with nested clades (that is, groups of haplotypes — linked alleles — that are arranged by successively increasing numbers of mutations). His analysis provides strong genetic support for describing the geographical centre of our species as African, with at least two major population expansions from that continent about 600,000 and 95,000 years ago. He also establishes a platform to make specific estimates for important parameters of population structure, including the level of gene flow between populations isolated by distance. As a strong supporter of the idea of an African origin for modern people, in the words of Hamlet, "I eat the air, promise-crammed".

Current limitations in the methods used to reliably extract ancient DNA[5] have led molecular geneticists to concede the direct study of the earliest stages of our lineage's history to palaeoanthropology. So events well before 2 million years ago remain the province of those who hunt for and interpret fossil remains. But there is also a contentious debate over modern human origins that centres on the time period from 1.7 million to 20,000 years ago and the emergence of anatomically modern people. Genetic diversity in the human population today is consistent with a model of expansion, predominantly from Africa, between 100,000 and 50,000 years ago. From this breeding population of as few as 10,000 individuals, there followed a second expansion in Europe about 21,000 years ago[6,7].

Oscillations in climate are assumed to have resulted in an increased isolation of different groups, which would have promoted the 'fixation' of local adaptations in morphology, physiology and behaviour. Geographically distinct populations in Europe, Africa, South Asia, China and Australia could have had separate evolutionary trajectories if there were not enough migrants in each generation to spread any new mutations to populations in other regions. Proponents of multiregionalism believe that, after the initial expansion from Africa, populations continued to evolve