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Curr Opin Cell Biol. Author manuscript; available in PMC 2020 March 27.

Published in final edited form as:
Curr Opin Cell Biol. 2016 August 01; 41: 43–50. doi:10.1016/j.ceb.2016.03.016.

Mixing and matching nuclear envelope remodeling and spindle assembly strategies in the evolution of mitosis

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Abstract

In eukaryotes, cellular genome is enclosed inside a membrane-bound organelle called the nucleus. The nucleus compartmentalizes genome replication, repair and expression, keeping these activities separated from protein synthesis and other metabolic processes. Each proliferative division, the duplicated chromosomes must be equipartitioned between the daughter cells and this requires precise coordination between assembly of the microtubule-based mitotic spindle and nuclear remodeling. Here we review a surprising variety of strategies used by modern eukaryotes to manage these processes and discuss possible mechanisms that might have led to the emergence of this diversity in evolution.

Introduction

The nucleus is delimited by the membranous nuclear envelope (NE) containing two apposed lipid bilayers. Of these, the outer nuclear membrane (ONM) is continuous with the endoplasmic reticulum (ER) and the inner nuclear membrane (INM) faces the intranuclear space and organizes an underlying protein meshwork of the nuclear lamina. The two membranes connect at the nuclear pores, communication channels between the nucleus and the cytoplasm decorated by the nuclear pores complexes (NPCs). The symmetrical NPC core is formed by nucleoporins that share common evolutionary roots with membrane-bending vesicle coat proteins. Peripheral Phe-Gly (FG)-repeat nucleoporins residing at the pore aperture ensure selectivity of nucleocytoplasmic transport along with the Ran GTPase system and other soluble factors. Remarkable conservation of most NPC components suggests that the last eukaryotic common ancestor (LECA) already had a functional nuclear envelope (for reviews see [1–3]).

A number of other proteins and protein complexes contribute to NE function. LINC (linkers of nucleoskeleton and cytoskeleton) complexes made of an INM-anchored SUN and the ONM-bound KASH proteins couple the chromatin to cytoplasmic cytoskeletal arrays and stabilize connections between the two membranes under mechanical load (for review see [4]). The SUN proteins also interact with other INM proteins and the nuclear lamina, which in turn organize chromatin at the nuclear periphery and supports NE structure and function (for review see [5]). Although functionality of the lamina is evolutionarily conserved, its molecular composition can vary substantially between species. Intermediate filaments

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lamins form the lamina meshwork in metazoans and proteins with similar structural motifs and functions have been recently discovered in other eukaryotic supergroups including protozoans, excavates and plants [6–8]. In organisms that lack lamin-like proteins altogether, lamina functions are likely performed by INM constituents, in particular the LEM-domain proteins. Yeast LEM proteins span the INM twice, with both the chromatin-interacting N-terminal LEM (or, rather its helix-extended loop-helix version) and the C-terminal MSC (MAN1–Src1p–C-terminal) domains facing the nucleoplasm. Proteins with similar architecture are found in all eukaryotic supergroups, indicating their ancient origin. The LEM proteins in yeast support NE integrity, organize chromatin at the nuclear periphery and regulate gene expression [9–14].

Eukaryotic chromosomes are segregated by a bipolar cytoskeletal array called the mitotic spindle. This structure containing microtubules, microtubule motors and other associated proteins, usually assembles at mitotic entry. Various spindle assembly mechanisms observed in different species can be categorized as either intranuclear or cytoplasmic. Intranuclear assembly - which often but not always accompanies a fully closed mitosis - implies that the spindle forms inside an intact nucleus. This requires that the mitotic microtubule organizing centers (MTOCs) are anchored at the inner side of the NE and that the tubulin dimers and microtubule-associated proteins are actively transported from the cytoplasm into the nucleus (for reviews see [15, 16]). Conversely, cytoplasmic spindle assembly relies on extranuclear microtubule nucleation and does not explicitly require delivery of the spindle constituents into the nucleus. This mechanism largely - but again not always - necessitates at least partial NE breakdown to enable access of spindle microtubules to the chromosomes.

The plethora of mitotic programs found in modern eukaryotes can be seen as a combination of these two spindle assembly strategies with distinct modes of NE remodeling (Fig. 1) [17, 18]. Here we examine natural variability in mitotic NE management focusing on the evolution of NE disassembly. Molecular mechanisms driving NE reformation after exit from mitosis have been recently discussed elsewhere [19, 20].

Mitotic NE dynamics in cells with intranuclear spindle assembly

During fully closed mitosis, the NE remains functionally intact, which may limit the availability of cytoplasmic MTOCs for spindle nucleation. Some organisms, such as the excavate *Trypanosoma brucei* solve this problem by building specialized mitotic MTOCs at the inner side of the NE (Fig. 1A; see [21] for review). Yet, many other organisms have invented a way to use the same MTOCs to organize cytoplasmic microtubules in interphase and nuclear microtubules in mitosis. The budding yeast *Saccharomyces cerevisiae* permanently anchors its spindle pole bodies (SPBs) within the plane of the NE, so that microtubules can be nucleated at both nucleo- and cytoplasmic sides throughout the cell cycle. Each cell cycle, the SPB duplicates and the daughter SPB is inserted alongside the mother (for review see [22]). Another model Ascomycete, the fission yeast *Schizosaccharomyces pombe* (*S. pombe*), keeps the SPBs at the cytoplasmic side of the NE in interphase and relocates them into the NE for the duration of mitosis, necessitating spatially and temporally confined NE opening, or fenestration (Fig. 1B and [23]). Mechanisms underlying MTOC placement within the NE and their regulation by the cell

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cycle machinery have been extensively discussed [15, 24]. While specific requirements may differ between systems, SPB insertion and anchorage overall rely on functional interactions between the transmembrane SPB component Ndc1/Cut11 (incidentally, also required for NPC anchorage) and NE components such as LINCs, the membrane shapers reticulon and Yop1, along with TMEM33 and Brr6 proteins that may aid membrane bending required for insertion by promoting specific lipid composition of the NE [25–32].

Intranuclear assembly of the mitotic spindle does not necessarily mean that the nucleus will remain intact for the duration of mitosis. The fission yeast *Schizosaccharomyces japonicus* (*S. japonicus*), a relative of *S. pombe* [33], starts mitosis in a manner very similar to its sister species but breaks the NE at the nuclear equator in anaphase (Fig. 1C and [11, 34]). Curiously, the NE remains fully functional up until the moment it breaks, as assessed by fully assembled NPCs and active nucleocytoplasmic transport [35]. Although the mechanism driving the NE breakage remains unknown, it appears to be controlled by the cell cycle machinery and further fine-tuned by interplay between the LEM-domain proteins Lem2 and Man1 and the mitotic spindle [11, 12].

Another Ascomycete that assembles the mitotic spindle from NE-embedded SPBs, *Aspergillus nidulans* (*A. nidulans*) also breaks the nuclear membrane in late anaphase [36]. In addition, it loses nucleocytoplasmic compartmentalization in early mitosis, downstream of mitotic CDK and NIMA kinase signaling. In a manner reminiscent of early events in nuclear envelope breakdown (NEBD) in metazoans (see below), the peripheral nucleoporins disperse from the NPCs, disrupting nuclear transport selectivity and presumably allowing tubulin, microtubule-associated proteins and other mitotic regulators to access the nucleoplasm (Fig. 1D and [37–39]).

Thus, cells building intranuclear spindles tend to maintain an intact nuclear membrane at least until anaphase. The nucleocytoplasmic transport may be abolished and the membrane may rupture later in mitosis but spindle assembly and kinetochore attachment proceed within the confines of the NE.

Mitotic NE dynamics in cells with extranuclear spindle assembly

This form of spindle assembly is found throughout the eukaryotic domain. At its simplest, the spindle remains cytoplasmic and chromosomes are segregated within an intact NE. In the core dinoflagellate group an extranuclear spindle passes through NE invaginations and makes indirect contacts with the chromosomes attached to the inner side of the NE (Fig. 1E). It appears that the kinetochore-like structures may be integrated into the NE [40–42]. If and how accurate chromosome segregation is ensured in cells where microtubules do not establish direct contacts with chromosomes remain unknown.

The flagellated green algae *Chlamydomonas reinhardtii* assembles a cytoplasmic spindle from the pair of polar organizing centers that form around cortex-associated basal bodies. The bulk of the NE remains unbroken but large polar fenestrae form to allow microtubule access to the chromosomes (Fig. 1F; for review see [43]). Similar strategy is utilized by the

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excavate *Giardia intestinalis* that divides its both diploid nuclei simultaneously by basal-body anchored spindles passing through large NE openings [44].

In fact, NE opening at the spindle poles allowing access of microtubules to mitotic chromosomes is widely spread in nature. Basidiomycetous budding yeasts *Ustilago maydis* and *Cryptococcus neoformans* undergo unusual mitoses as compared to their Ascomycete counterparts. In interphase *U. maydis* cells, SPBs lie on the outer side of the nucleus located in the mother cell. As cells enter mitosis, the NPCs disassemble and the nuclear membrane fenestrates in the vicinity of the SPBs. Astral microtubules emanating from the SPBs pull them together with chromosomes into the daughter cell, leaving the NE remnant behind (Fig. 1G). The spindle elongates in anaphase, pushing one set of chromosomes back into the mother cell [45, 46]. In *C. neoformans* a remnant of the mother NE is eventually utilized to enclose daughter genomes [47].

Early polar fenestration followed by further breakdown of the NE in anaphase occurs in some metazoan cells, e.g. in the embryos of the nematode *Caenorhabditis elegans* (Fig. 1H) and the fruit fly *Drosophila melanogaster*. Gradual NE breakdown in these cell types starts from complete NPC disassembly, with some INM and lamina constituents persisting at the nuclear periphery until late anaphase [48–50].

Finally, NE identity is completely lost in early mitosis in somatic metazoan and land plant cells. The process is best understood in cultured mammalian cells (Fig. 1I; see [51] for an excellent review). Phosphorylation of the peripheral nucleoporin Nup98 by mitotic CDK and other kinases triggers full NPC disassembly and a loss of nucleocytoplasmic compartmentalization [52].

CDK1 also phosphorylates lamins and lamin-associated proteins, promoting depolymerization of the lamin meshwork and chromatin detachment from the INM [53]. Lamina disassembly additionally destabilizes the nuclear membrane, making it more susceptible to microtubule motor-dependent tearing in the vicinity of spindle poles [54, 55]. Microtubules are not essential for NEBD but increase its efficiency, similarly to their function in fungi *S. japonicus* and *U. maydis*. LINC complexes [56] and ER proteins REEP3/4 [57] interact with microtubules to clear membranes away from chromatin.

Curiously, some degree of compartmentalization remains even in fully open mitosis. Membranes derived from the ER and the NE surround the mitotic spindle and may promote a specialized molecular crowding state in the vicinity of the mitotic apparatus [58]. This remaining compartmentalization may account for accumulation of soluble tubulin subunits and factors promoting microtubule assembly to assist timely spindle assembly and proper function [59].

Plasticity of NE remodeling in mitosis

A remarkable diversity of mitotic mechanisms that arose in evolution suggests that rewiring of NE behavior can be achieved with relative ease. In fact, as attested by organisms that switch between different types of NE remodeling and spindle assembly during their ontogenesis, mitotic plasticity can emerge form relatively minor tweaks in a conserved

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molecular machinery supporting nuclear integrity. A case in point is the myxomycete mold *Physarum polycephalum* that transits between a fully open mitosis with a cytoplasmic spindle in its uninucleate state and closed mitosis with an intranuclear spindle in syncytial plasmodium [60]. Thus, mitotic NE behavior can be viewed as a continuum of intermediate states, each reflecting a degree to which separate compartmental identity is maintained (Fig. 1).

There are several recurring approaches to perturb nuclear identity that likely reflect NE "vulnerabilities" exploited by mitotic regulators (Fig. 2). One of them may center on mitotic phosphorylation of peripheral nucleoporins, in particular an evolutionarily conserved FG nucleoporin Nup98, which triggers its dissociation from the nuclear pore [52]. Since Nup98 enforces NPC transport selectivity [61, 62], its removal renders the NE permeable, allowing intermixing between the nuclear and cytosolic compartments and optionally, further phosphorylation-dependent NPC disassembly. Introducing discontinuities into the nuclear membrane will result in a similar outcome, even if the NPCs remain assembled. This strategy may require fusion between the outer and inner membranes generating NE breaches that can further expand through interaction with the cytoskeleton. Finally, disassembly of an INM-organized lamina causing dissociation of the chromatin from the nuclear periphery may reduce the ability of the NE to withstand the considerable pushing or pulling forces exerted by the cytoskeleton.

These events are wired into the logic of the cell cycle, i. e. regulated by the mitotic driver CDK1 and other kinases active during mitosis (Fig. 2). Interestingly, CDK1, NIMA, Polo and Aurora family kinases implicated in NE remodeling in different experimentally tractable systems tend to be enriched at the spindle poles where nuclear membrane discontinuities are often initiated. Recent work suggests that the Polo kinase associated with mitotic chromatin may promote localized NE breakdown in *C. elegans* embryos [63], underscoring that the cell cycle machinery may regulate NE integrity in a spatially constrained manner. Evolution of networks determining NE fate during mitosis may proceed in *cis*-, by evolving proteins with somewhat different properties including distinct capacities for phosphoregulation. For instance, some of the mitotic phosphosites identified in mammalian Nup98 are conserved in *A. nidulans* but not in yeast species undergoing closed mitosis [52]. Alternatively, fairly identical biochemical machinery may be plugged into different regulatory circuits resulting in distinct functional outcomes, as in the lipin-centered pathway of NE expansion required for closed mitosis [64].

Factors affecting the choice between different mitotic mechanisms

What could be the reasons for mitotic diversity? First, it is worth considering that, in a given system, evolution of nuclear division may be constrained by factors unrelated to mitosis. Mitosis is often thought as "efficient" when chromosomes are segregated faithfully, rapidly and with minimum energy consumption. While this is generally true, ramping up the proliferation rate may lower the overall fitness of an organism due to a number of reasons, including, at its simplest, reallocation of finite resources between cell division and other critical processes. The mitotic machinery may also have functions beyond chromosome segregation. As an example, the mitotic spindle is important in determining the site and

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plane of cytokinesis in multicellular organisms [65] so NE breakdown could enable spindle-mediated signaling to cell division machinery located outside of the nucleus. Mitosis may further help to segregate structures and organelles other than chromosomes and specific spindle architectures and NE topologies may facilitate this functionality. For instance, emergence of the cytoplasmic spindle organized by centriole-structured MTOCs may have been an evolutionary cooption driven by pressure to segregate basal body-based cellular motility systems. Co-segregation of genomes and the basal bodies may have been economical but it also necessitated opening up the NE to allow cytoplasmic microtubules to access the kinetochores. This in turn generated a potential for evolving corresponding physiological and environmental regulation mechanisms.

There could be several general considerations driving selection of a particular mode of mitosis. Rapid and/or syncytial divisions tend to occur in a closed or semi-open manner, with the bulk of the NE maintaining its separate identity. For instance, the nuclear membrane remains largely intact in fast S/M cycles in green algae and cleaving embryos, in addition to many rapidly dividing unicellular organisms (Fig. 1). This strategy could have been selected to prevent entanglement of the neighboring spindles and chromosome mis-segregation in a multinucleate environment but also to accelerate resealing of the NE in the daughter nuclei. In addition to reducing the time between subsequent divisions, the latter may protect the genome from possible risks including reactive oxygen species and foreign genetic elements [66]. The sheer geometry of closed nuclear division could also contribute to daughter cell differentiation by promoting asymmetric segregation of episomes [67] and other nuclear components [68]. This could be particularly important for free-living microbes directly exposed to the environment.

But why not keep the nucleus always intact? In a syncytium, breaking down the nuclear selectivity barrier can enable fast mitotic signaling throughout the common cytoplasm and facilitate diffusion of spindle components inside each individual nucleus. Further considerations could include a high cost of nuclear membrane expansion required for fully closed division. Intact nuclei need to increase their surface area to accommodate division into two daughters – in fact, such mitotic NE expansion has been observed in a number of experimental systems including the fission yeast *S. pombe* [11, 69]. The NE does not expand in its sister species *S. japonicus*, necessitating membrane breakage to build two smaller daughter nuclei [11]. For these two organisms, divergent regulation of phosphatidic acid flux by the phosphatidic acid phosphatase lipin appears to underpin differences in mitotic NE expansion [64]. Energy cost may become prohibitive in cells with large genomes and correspondingly larger nuclei because of a sharp increase in absolute amount of membrane required to enclose DNA. Fully closed division may also rely on specific adaptations to prevent abnormal NE distortion by an elongating anaphase spindle, a function executed by the SPBs in fission yeast [70, 71].

Genomes with large size and complexity may favor a fully open mode of mitosis for a number of reasons. First, it may be difficult to capture, align and segregate a large number of kinetochores in an enclosed compartment. Second, building a large spindle through active transport of tubulin monomers and accessory factors may be inadequately slow. Finally, differences in scaling between the nuclear diameter and spindle length as related to genome

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size may preclude assembly of an intranuclear spindle predicted to become too large to fit into the nucleus beginning from a certain genomic size [66].

How an ancestral eukaryote might have divided its nucleus remains an important question, albeit difficult to answer in the absence of fossil record. The abundance of semi-open mitoses in all modern eukaryotic supergroups, together with their relative simplicity as compared to fully closed or fully open divisions, suggests that an ancestral eukaryote might have divided its genome through partially breaking the NE. It may have used nuclear membrane elaborations to move chromosomes on extranuclear cytoskeletal arrays that could have been based on actin or microtubules. Specialized mitotic spindle, as we know it, is likely a later invention. The half-spindles of dinoflagellates interacting with chromosomes through the NE potentially represent a vestigial transition stage between ancient and modern chromosome segregation strategies. A shift towards spindle microtubules as a primary force to move chromosomes should have improved their segregation fidelity [18] and culminated in the emergence of a modern kinetochore and the spindle assembly checkpoint. Still, kinetochores remain associated with the MTOCs throughout the cell cycle in many modern unicellular eukaryotes and a number of NPC components moonlight on kinetochores during chromosome segregation in more complex organisms (see [42, 72] for reviews). The *S. pombe* nucleus can even divide without spindle microtubules, as long as kinetochores-SPB interactions are maintained [73].

An ancient membrane remodeler ESCRT-III has been recently implicated in NE reformation following mitosis in cultured mammalian cells [74, 75]. Given that it is involved in other NE-based processes such as NPC quality surveillance [76], it would be important to evaluate if it supports mitotic NE dynamics in other organisms. The fact that the machinery that executes final steps of cytokinesis in eukaryotes and archae is involved in membrane fusion events at the NE suggests intriguing insights into evolutionary origins of the NE and mitosis. A recent “inside-out” hypothesis on the origin of eukaryotes, postulates that the eukaryotic endomembrane system may have evolved from the plasma membrane protrusions of an archaeal host cell that eventually became the nucleus, co-evolving with an ensnared α-proteobacterium that became a proto-mitochondrion [77]. According to this hypothesis, nuclear division in an early proto-eukaryote would be similar to archaeal cytokinesis, indeed placing the ESCRT-III machinery at the core of nuclear membrane remodeling.

Outlook

To conclude, there is a lot of interesting biology to learn by studying how mitotic nuclear remodeling has evolved throughout the eukaryotic domain of life. First, it may inform our understanding of basic NE biology and indeed, nuclear origins. Second, it may tell us how variation arises at the cellular level, essentially linking cell biology to evolutionary analysis. Such studies can be particularly powerful when conducted mechanistically in related organisms that utilize distinct approaches to mitosis. As an example, comparative analyses using the fission yeasts *S. pombe* and *S. japonicus* have been instructive in illuminating functional requirements for closed mitosis and division site positioning [11, 64, 78, 79]. Importantly, retroengineering recombinant and synthetic mitotic systems with novel properties should improve our understanding of how specific mechanisms of nuclear

division interact with other physiological pathways. Current advances in genome editing, genome analysis and other “omics” approaches will undoubtedly streamline such experiments, finally putting answers to long-standing evolutionary questions within our reach.

Acknowledgements

We are grateful to Oliferenko lab members for discussions and E. Makeyev for suggestions on the manuscript. Our work is supported by a Wellcome Trust Senior Investigator Award (103741/Z/14/Z) to S. O.

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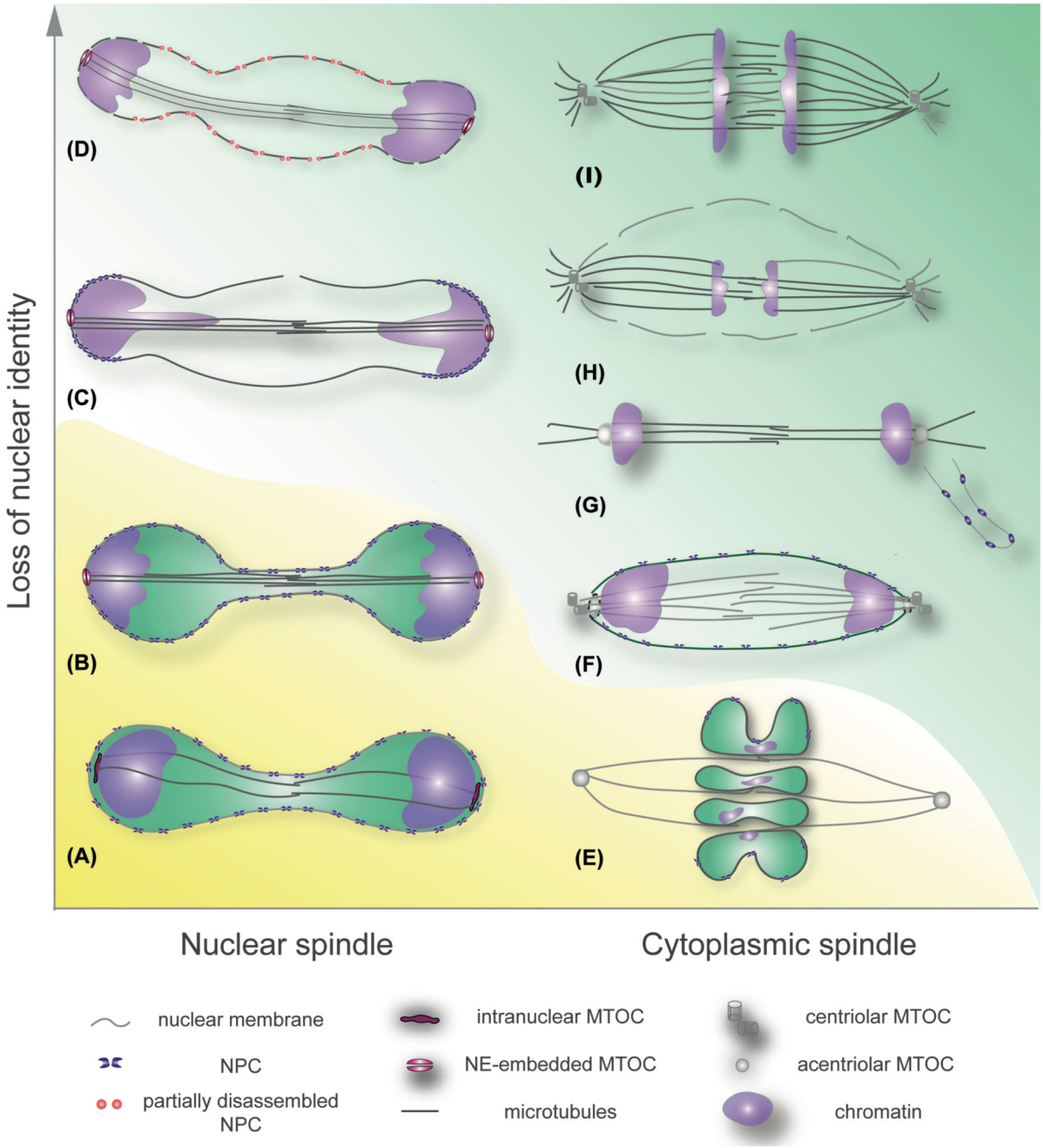

Figure 1.

Diagrams summarizing representative modes of mitosis across eukaryotes. The mitotic apparatuses are shown in anaphase. Left column: (**A**) the excavate *Trypanosoma brucei*, (**B**) the fission yeast *Schizosaccharomyces pombe*, (**C**) the fission yeast *Schizosaccharomyces japonicus*, (**D**) the filamentous Ascomycete *Aspergillus nidulans*. Right column: (**E**) the dinoflagellate *Crypthecodinium cohnii*, (**F**) the green algae *Chlamydomonas reinhardtii*, (**G**) an yeast form of the Basidiomycete *Ustilago maydis*, (**H**) an embryo of the nematode *Caenorhabditis elegans*, (**I**) a cultured human cell. Yellow background indicates “closed”

modes of mitosis and green background denotes mitotic NE breakdown. Pictorial legend is shown below.

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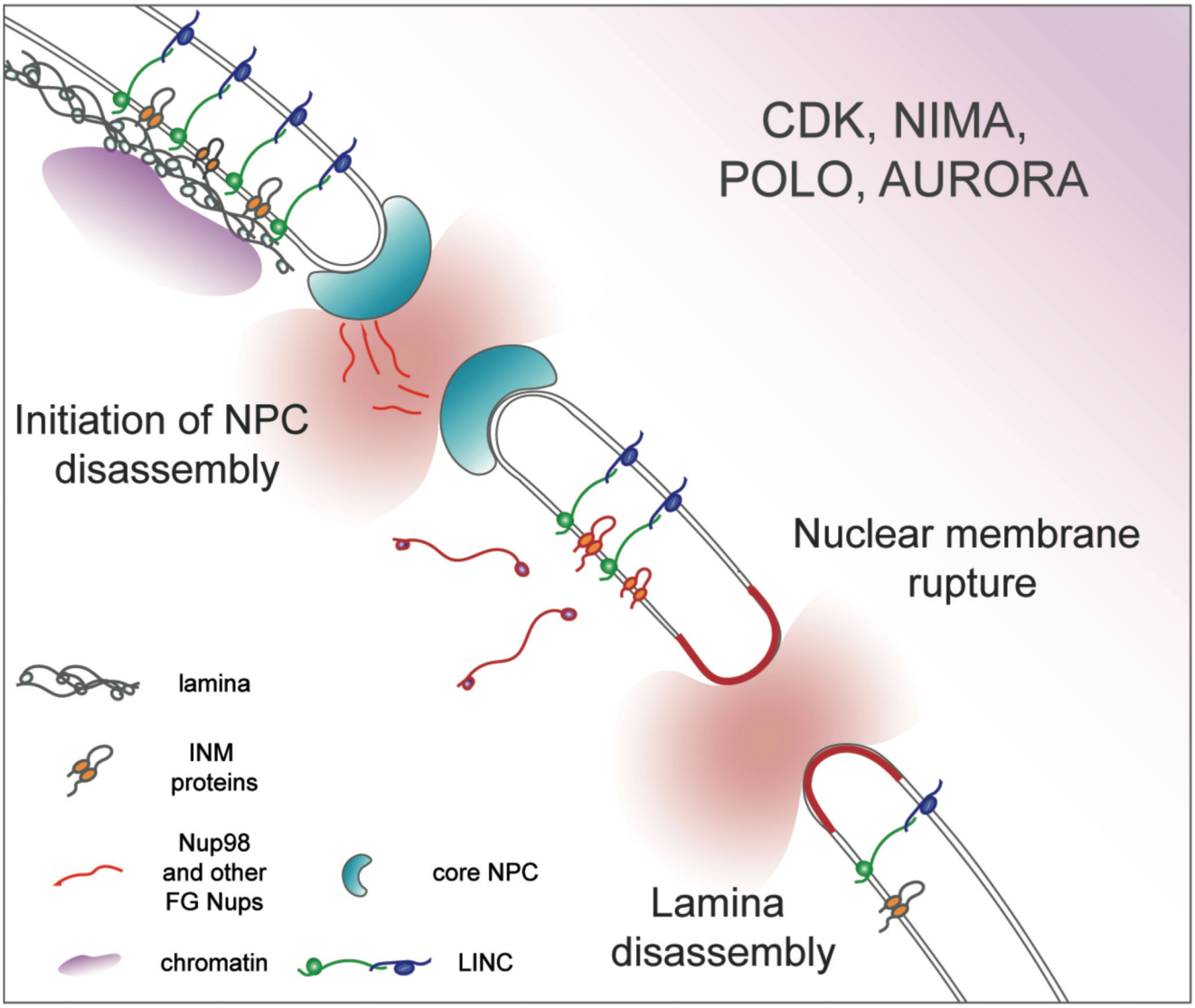

Figure 2.

A schematic diagram describing NE "vulnerabilities" (e.g. NPC selectivity, membrane integrity and lamina function, outlined in red) that can be attacked by mitotic regulators (e.g. CDK1, Aurora, Polo and NIMA kinases) to induce NE disassembly or remodeling. Pictorial legend is included.